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THE CHARACTERISTICS OF NORMAL HEART SOUNDS RECORDED BY DIRECT METHODS

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INTRODUCTION

PHONOCARDIOGRAMS serve the useful purpose of inscribing transient acoustic phenomena as permanent records which can be analyzed and studied at leisure. Their increasing use in research and teaching, and even as an auxiliary to auscultation in diagnosis, demands that the sounds be recorded with the greatest fidelity possible, or, at least, that the errors introduced be known and recognizable. Since the character of sound records depends to a considerable extent upon the apparatus and the technique employed in their registration, a consideration of the question as to what constitutes the best practice cannot be avoided. This becomes especially necessary because different authorities not only favor the use of different types of apparatus, but continue to utilize entirely different physical principles in operating the same type of recorder.

TECHNICAL DEVELOPMENTS AND THEIR LESSONS

By the use of a carbon microphone, a secondary coil amplifier, and a recording electrometer, and later a string galvanometer, Einthoven and his associates[1, 2, 3, 4] set a standard for registration of human heart sounds with which other methods were not able to compete for many years. In 1905, O. Frank[5] developed his well-known *segment capsule* to replace an earlier and more complicated device resembling the middle ear and its ossicles. Its lack of sensitivity, however, precluded its use in the registration of human sounds, except in very emaciated subjects, and even then the records were not entirely unsatisfactory. In 1917, Wiggers and Dean[6] made these capsules more sensitive by

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covering them with a delicate film of rubber cement, upon which a tiny mirror was placed. They also enclosed the membrane within a housing which had a glass window and a small vent. The housing served the double purpose of protecting the membrane from room noises and of partially damping its free oscillations. The routine use of such recorders for over twenty years in this laboratory has demonstrated that they are sensitive enough to register normal sounds satisfactorily, provided the connecting tube is not over 70 cm. in length. Records thus obtained are not entirely free from coarser vibrations of the chest wall or other thoracic noises, but sufficiently so that the two ventricular sounds can be easily differentiated. In addition, a small preliminary wave preceding the first sound is clearly recognizable in many records.

Investigators who used these capsules were required to learn the technique of making new membranes, which is simple, and to train their eyes to discount the adventitious vibrations which appear in the intervals between the sounds. These intervening vibrations are bothersome, however; first, because they sometimes prevent recognition of murmurs, and, second, because they tend to summate with true heart sound vibrations, thus raising the suspicion that the sound complexes contain vibrations other than those which belong to them. The desirability of silencing the intervals between sounds has long been appreciated, but the problem has been to accomplish this without eliminating some of the inherent vibrations of the heart sounds at the same time.

The rapid development and improvement in electron tube amplifiers, microphonic receivers, and electrical filtration suggested to many in Europe and in North and South America that most of the previous difficulties inherent in electrophonic sound registration might be overcome by an assembly of the proper apparatus. As a result, a considerable number of electrophonocardiographs have been described, and quite a few are commercially available. The apparatus described by Lockhart and his associates,[7] in 1935, and subsequently improved,[8] is probably the best known in the United States. It can be taken as an example for discussing, not the mechanisms of sound registration, but the devices used to eliminate adventitious oscillations from the records. By restricting the easily recordable frequencies to ranges encountered in heart sounds themselves, many coarser mechanical vibrations, always present in the chest wall, are probably eliminated satisfactorily. But in the electrophonic method, as in the direct methods, there still remains the problem of how to eliminate adventitious sounds and noises constantly present in the chest. These are caused in part by respiration, in part by movements and changing contacts of the beating heart, and in part by filling and emptying of the ventricles. Together, they create a continuous stream of vibrations which are sub-

liminal as far as hearing is concerned, or at least can be willfully excluded, but easily affect sound-recording systems. Electrical filtration has not proved to be a satisfactory method of eliminating them, apparently because their periods are within the same ranges as those of heart sounds. Hence, the same general expedients which are necessary to eliminate these adventitious sounds with direct methods of sound recording must be used with electrophonic registration. Only one principle is really serviceable, viz., that of reducing the sensitivity of recorders so that they, like the human auditory mechanism, do not respond to these noises. In electrophonic recorders, such reduction in sensitivity can be accomplished by reducing thermionic amplification by means of selective chest pieces, by more complete pressure equalization between the interior of the tube and the air, etc.

Judicious application of such principles, and perhaps of others, has made it possible to construct electrophonic recorders which eliminate such noises. The question arises, however, whether a part of the audible sounds is, perhaps, eliminated at the same time, with the result that the recorded group may not contain its full complement of vibrations.

Consequently, despite the superiority of modern electrophonic apparatus as regards portability, readiness for service, and simplicity in operation, it cannot be accepted without further proof that the types of records commonly exhibited and published give as reliable pictures of the heart sounds as do those obtained by direct methods, when the latter are properly used.

Concurrent with improvements in electrophonic registration of heart sounds, progress was made in the development of direct modes of registration. In 1937, one of us (Eckstein[9]) found that the vibrations recorded between heart sounds can be minimized, or even entirely eliminated, by making slight but essential changes in the Wiggers-Dean recorder. Briefly, these consisted in (1) stretching the dried rubber cement membrane so that its frequency was increased to 350, or more, per second; (2) vulcanizing the membrane by exposing it to SCl_4 vapor, thus increasing its permanence; and (3) enlarging the side-tube opening to the air, thus preventing many adventitious chest noises from reaching the membrane. Efforts were also made to increase the decrement of vibrations by adding damping devices. The latter were important for the projects then under investigation, but for the recording of human sounds they offer no advantage and sometimes prove to be an encumbrance. Simple tests have shown that the larger side opening does not admit room noises under average conditions of quietness.

These procedures which were adopted to enhance the *figure of merit* of the recording capsule and conducting tube necessarily reduced the sensitivity of the apparatus for normal sounds. This was compensated

for by adopting the expedient of Hamilton, Brewer, and Brotman,[10] which consisted in projecting the beam of light upon a small planoconvex mirror (ca .75 diopter), silvered on the plane side, and in focusing the beam upon a photokymograph 3 to 5 meters distant. More recently, we adopted the expedient of Green,[11] i.e., of replacing the window in the housing by a planoconvex lens of proper focal length, and using plane mirrors. This obviates the trouble of procuring planoconvex mirrors of exactly the same focal length when multiple registrations are desired; it also makes it possible to use thinner mirrors on the membranes. In this way a sensitivity somewhat greater than that of the original Wiggers-Dean capsule could be realized, while the natural frequency was considerably enhanced (100 or 150/sec. $<$ 300 or 400/sec.).

While we were proceeding in the direction of enhancing the frequency, reducing the periodicity, and slightly increasing the original sensitivity of the Wiggers-Dean recorder, Orías and his various associates were moving in an opposite direction (for references see Orías and Braun-Menéndez[12]). They removed the soundproofing housing, utilized looser membranes, and modified their consistency and flexibility by adding a small amount of paraffin oil to mixtures of rubber cement. In addition, they applied a larger receiver (ca. 6 cm. in diameter) over the chest, thereby registering sounds from a more diffuse region, rather than from a limited area, as in auscultation and by our system. In these ways, sensitivity was increased tremendously; in fact, with a projection distance of 1 meter, two vents could often be used for eliminating mechanical vibrations and adventitious noises. But these procedures greatly reduce the frequency of their capsules, in some cases to less than 20/sec. In addition, the membranes are so periodic that unless mechanical jars are *completely* eliminated through open side tubes, the membranes are set into vibration at their own frequencies.

Despite this backward step, as regards reduction in the *figure of merit* of capsules, Orías and his various associates,* through the use of such apparatus, broadened our knowledge of heart sounds and enlarged the field of usefulness of phonocardiography. They presented evidence that four sounds are far more common in normal subjects than had been generally realized. They analyzed various components of these sound groups and reached the logical conclusion that many well-known auscultatory signs of disease are merely exaggerations of sound components present in normal hearts.

After careful consideration of their graphic evidence, and especially after frank, critical, and pleasant discussions between the Argentine investigators and one of us (C. J. W.) during a recent visit to Cordoba, we agree that many of their conclusions seem logical and probable.

*Allende, Battle, Battro, Braun-Menéndez, Caeiro, Cossio, Garguilo, Maldonado, Martinez, Pereira, Pérez, Segura, Solari, and Taquini (for references see Orías and Braun-Menéndez[12]).

However, records obtained by their modified sound capsules are complicated by so many adventitious vibrations that interpretations often become a matter of opinion. Thus, the periods of atrial and third sounds are often quite similar to those which occur at other parts of the cycle, and periods recur throughout the records which are suspiciously similar to the estimated periods of their loose membranes. The criticism which O. Frank offered so vigorously in the case of the instrument developed by Weiss might equally well be applied here. Furthermore, since the ribs, intercostal spaces, and sternum, and, indeed, the whole body, receive an impact during atrial systole and during rapid ventricular filling, the possibility is not eliminated that these jars might have set their highly undamped membranes into oscillation. Consequently, while their interpretations are probable, the Argentine investigators have not demonstrated with certainty that some of the vibrations recorded did not arise in the apparatus rather than in the heart or chest.

In any event, the assertion that four distinct sounds commonly occur would be more convincing to us if it could be shown that they are also recordable in a fair percentage of normal subjects by capsules that are more highly damped and have a higher frequency.

COMPARISON OF SOUNDS RECORDED BY CAPSULES WITH LOWER AND HIGHER FREQUENCIES

A valid comparison of sounds recorded by different methods is much more difficult than is commonly realized. In the first place, sounds used for comparison must be selected in the same phase of respiration and also in the same phase of a sinus arrhythmia, when the latter is present, for the configuration of normal sounds varies from beat to beat. Theoretically, sounds should be recorded simultaneously from the same chest piece, for their character depends upon its diameter and shape, as well as its location, apposition, and pressure on the chest. This precludes comparison of different methods, such as the direct and electrophonic, which necessitate the employment of different receivers. It also precludes simultaneous registration from different areas, even when these are adjacent.

PROCEDURES

In fifty medical students, who were in their early twenties, we recorded sounds over the precordium, using the same receiver, by means of capsules with loose, and capsules with taut, membranes. Such capsules had frequencies of from 30 to 50/sec. and 175/sec., respectively. This restricted range was necessary in order to register both curves satisfactorily on a photokymograph placed at a fixed distance of 3 meters. When the membranes of lower frequency capsules were made looser, the sounds were too large for registration at a camera distance of 3 meters, and when the membranes of the higher frequency capsules were made more taut, satisfactory curves could be recorded only by moving the camera 5 meters away.

In some cases, records were obtained with two capsules simultaneously, but inasmuch as the influence of the lower frequency capsule upon the higher frequency membrane could not be eliminated with certainty, our best comparisons were obtained from records made in rapid sequence, care being taken to select comparable beats in respiratory and arrhythmia cycles.

All subjects were studied while they were in the recumbent position. An obtuse wooden receiver (3 cm. diameter) was placed over the apex, after applying a thin layer of petrolatum to secure constant apposition with the skin. The receiver was held by a weakly elastic band, which encircled the thorax and stretched easily with respiration. Its connections with two capsules of differing sensitivity through tubes 70 cm. long, and with a stethoscope for auscultation, are shown schematically in Fig. 1. By clamping at *X*, *Y*, and *Z*, by means of a hemostat, one or any combination of the three systems could be employed. When desired, an apex-beat recorder could be substituted for one of the sound capsules.

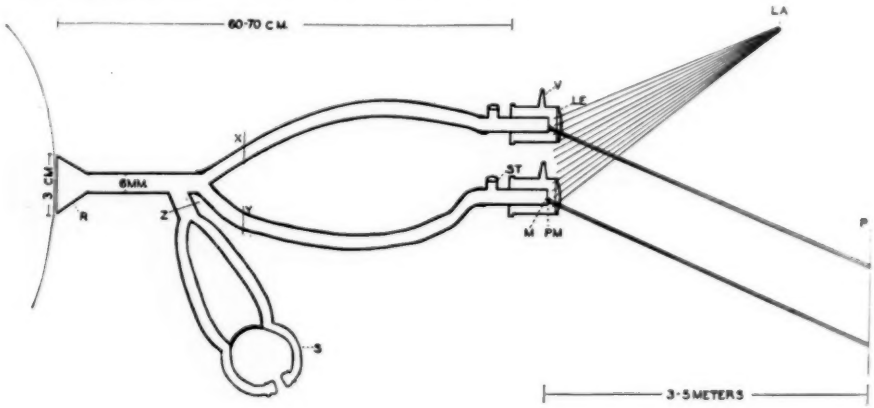

Fig. 1.—Scheme (not to scale) of the arrangement for recording duplicate heart sounds by direct methods. *S*, stethoscope that can be damped at *Y*; *M*, rubber cement membrane; *PM*, plane mirror; *LE*, planoconvex lens; *V*, pressure-equalizing vent for housing; *ST*, opening to exterior.

The venous pulse was recorded simultaneously. This served as a reference curve for dynamic events and for indicating phases of respiration. As has been emphasized by Orías and his associates,[12] such a venous pulse tracing offers the best means of establishing the temporal relations of sounds to atrial and ventricular events. The electrocardiogram gives no indication of diastolic events, and P, R, and T waves bear a variable relation to dynamic events. However, corrections must be made for the time required to transmit sounds and pulses through the tubing, and, in the case of the venous pulse, allowance must also be made for the transmission of pressure waves to the neck. This correction has not been strictly carried out by some investigators. A correlation of curves can be accomplished in a simple way, because of the fortuitous fact that the second sound appears distinctly at the base of the V-wave in the venous pulse, as well as in the sound record. Indeed, this sound is so constant in the human venous pulse that the adequacy of the hidden pulse recorders of commercial instruments can be checked by the occurrence of such vibrations.

In Figs. 2 and 3, line *2* indicates the relations of sounds to coincident pressure changes as they occur in the right atrium. By marking off equidistant points and drawing other lines, such as are indicated in these figures, the relationships of other sounds to dynamic events of the cardiac cycle can be established, regardless of delays in transmission by tubing or vessels.

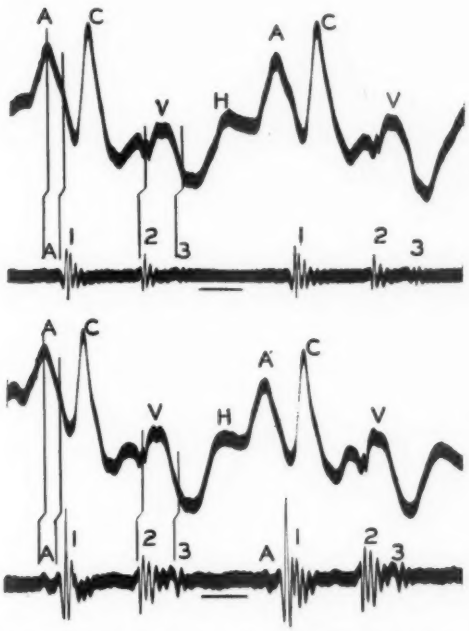

Fig. 2.—Two sets of venous pulse and heart sound tracings. Upper set, "taut-membrane" capsules; lower set, "loose-membrane" capsules. The horizontal line denotes ⅕ sec.; the vertical lines show time corrections (discussion in text).

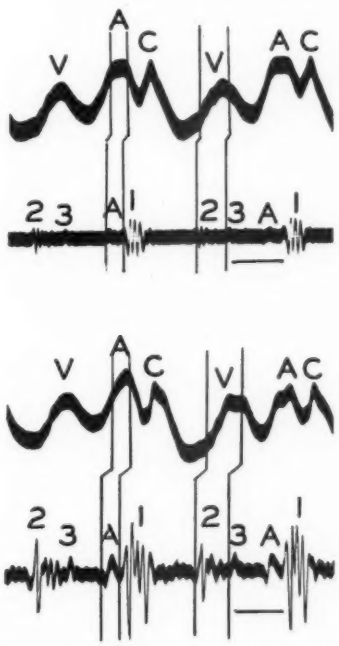

Fig. 3.—Records and labeling same as in Fig. 2. Note variability of first sound in successive beats (discussion in text).

It must be noted, however, that the venous pulse records events in the right side of the heart, whereas sounds recorded at the apex are chiefly caused by left-sided events. The turning points of the A wave, for example, are about .02 second later in the left atrium, and the possibility is always present that the contractions and ejections of the two ventricles may not occur quite simultaneously. Despite these handicaps, the venous pulse represents the most reliable curve that can be used for comparison in human beings.

RESULTS

Figs. 2 and 3 show two sets of sound records related to venous pulse waves; those in the upper records were recorded by "taut-membrane capsules," and those in the lower ones by "loose-membrane capsules." These records were chosen because they display four sets of vibrations, known as the atrial, first, second, and third heart sounds. The lower record of Fig. 2 shows, by the wavy character of its base line, that mechanical impacts were not completely eliminated. The differences in the number of vibrations and the general appearance of the two first sounds offer an example of the manner in which the character of the first sound can easily be modified during the acts of respiration. The lower record of Fig. 3 illustrates a curve in which mechanical impacts are less conspicuous, but the intervals between sounds contain numerous smaller vibrations caused by chest noises. These, however, are less conspicuous than those found in records published by investigators who eliminated the protective housing. Despite these impurities, such records allow definite recognition of the four sounds and are satisfactory for many purposes.

The sounds recorded by "taut-membrane" capsules from the same areas, shown in the upper curve, illustrate the effect of clearing such records of all extraneous noises. The sounds themselves consist of a more regular series of vibrations, but the vibrations are smaller in amplitude and fewer in number. They closely resemble the "filtered" sounds recorded by electrophonic recorders. Aside from these differences, the records taken by "loose-membrane" and "taut-membrane" capsules are essentially alike. Calculations of the vibration periods of individual oscillations show that the frequencies are nearly the same. However, other records taken with capsules having a frequency of 350/sec. contain a few oscillations of shorter periods. Projection of the sounds upon the venous pulse curve shows that the time relations are the same in the two types of registration. Hence it is improbable that errors in temporal placement of sounds are incurred through the use of "loose-membrane" capsules. The suspicion entertained by us that certain components, or whole sounds, such as the atrial and third sound, are caused by vibrations set up in loose membranes, rather than in the heart, seems to be without foundation, for they are also present in records taken by "taut-membrane" capsules in which the intervening intervals are silent (upper records, Figs. 2

and 3). This statement should not be interpreted as implying that such inherent oscillations of the membrane cannot complicate recordings; we merely affirm that, with the proper technique, this is not a necessary drawback to the use of "loose-membrane" capsules.

The chief advantages of "taut-membrane" capsules, with higher natural frequencies, are (1) that a few vibrations with shorter periods are recorded in the first sound complex, and (2) that records can be cleared more easily of vibrations between groups of sound vibrations. However, the smaller number of vibrations recorded and their smaller amplitude create the suspicion that some of the vibrations actually belonging to the heart sounds are, at the same time, repressed. A careful study of our own records, as well as those of others recorded by electrophonic methods and proudly exhibited as true pictures of sound components, has convinced us that incomplete heart sounds are registered more frequently than is commonly suspected. Indeed, unless caution is exercised in clearing records of adventitious vibrations, even errors of interpretation can arise. An instance is shown in the record of Fig. 4. If we were to examine such a sound tracing by itself, the conclusion would probably be reached that a short first sound is preceded by an atrial sound. However, its time relations with respect to venous pulse waves show clearly that all of the vibrations belong to the first ventricular sound.

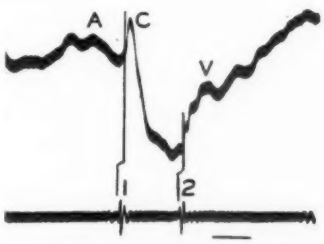

Fig. 4.—Venous pulse, intra-auricular type, and "overfiltered" heart sounds, showing error that may occur.

No other conclusion is possible than that the danger of recording abnormal sounds through "overfiltration" is fully as great as that incurred by having a few extraneous vibrations between the sounds. In any event, we desire to stress the point that, regardless of the method used, it should be the *primary aim* to reproduce the vibrations of sounds as fully as possible, rather than to record curves with silent periods. Achievement of the latter is admittedly desirable, but it must remain a secondary, not a primary, objective. Above all, it certainly does not constitute a guarantee that the recorded heart sound vibrations are those emanating from the chest.

With this dilemma before us in heart sound registration, it is our recommendation, backed by considerable experience, that a *series of records*, in which mechanical and adventitious noises are eliminated to

different degrees, but including one, similar to that of Fig. 5, in which the curves are almost, but not quite, cleared of these vibrations, should be made on every subject. However, although general principles and rules may be useful, the registration of heart sounds remains a specialized undertaking requiring training, experience, and judgment. Despite the availability of improved apparatus, which is easy to operate, the day has not arrived when heart sounds can be recorded routinely through simple maneuvers, as is the case in making electrocardiograms. Finally, in view of the astounding changes in the configuration and vibrations of sounds which are produced by even slight changes in technique, it is improbable that repeated records from patients will prove to be of much diagnostic or prognostic importance for clinicians or practitioners of medicine. The chief value continues to remain in fields of research and teaching.

TIME RELATIONS TO CARDIODYNAMIC EVENTS

The time relations of the four sounds to cardiac events, which are mirrored in venous pulse tracings, again merit brief comment, for upon them depend theories regarding their causation. It is a truism that no sound can be caused by an event that does not occur at the time that the sound starts.

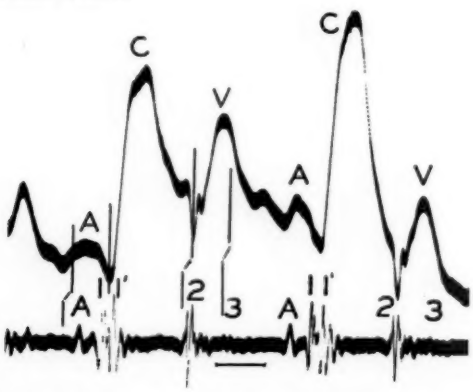

Fig. 5.—Venous pulse with large arterial impact, showing relation of second sound to incisura. Sound record obtained with fair degree of "filtration." Note double set of first sound components, labeled *1* and *1'*.

The small presystolic (atrial) vibrations are never evident before the peak of the A wave in the atrium (Figs. 2, 3, and 5). This signifies that they arise when the force of atrial contraction is on the wane and extend into the early phase of atrial relaxation. These time relations definitely preclude the possibility that they may be caused by muscular contraction of the atria per se. The same is true of the dissociated atrial sounds which are recorded and heard in cases of complete heart block.

The question of whether or not they really originate in the heart appears to be settled by the fact that they are occasionally present in records taken directly from the exposed ventricles of dogs. Such a record, correlated with changes in left ventricular pressure, is shown in Fig. 6. Time comparisons indicate that these sounds begin definitely before the rise of intraventricular pressure, but may continue slightly into the early period of rising tension. However, that portion of the presystolic run of vibrations which does continue has a shorter half period than the others and, therefore, represents the initial vibration of the first ventricular sound, rather than the termination of the atrial sound. This is supported by the frequent observation that such a vibration introduces the first sound complex in complete heart block, i.e., when ventricular contraction is not immediately preceded by an atrial beat. While this initial wave of the first sound can be picked out rather exactly when some other curve, such as the ventricular pressure in the dog (Fig. 6), or the human venous pulse,* is recorded simultaneously, it is often difficult to say, from sound records alone (e.g., Fig. 7 or 8), which of several points marks the precise moment at which ventricular systole begins.

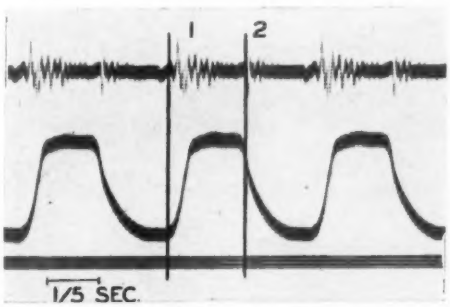

Fig. 6.—Sounds recorded directly from dog's ventricle by punctate pickup receiver, and relations to left intraventricular pressure curve (discussion in text).

Orías and his associates[12] point out that the character of the vibrations composing the first sound frequently changes at the time of ejection. We have noticed this in a small number of normal subjects; an example is shown in Fig. 5, in which the components are labeled *1* and *1'*.

The second sound coincides with the initial drop of pressure during protodiastole (Fig. 6), or with the bottom of the incisura of the aortic pulse (Fig. 5), and with a similar set of vibrations in the venous pulse which have already been described as our index of time relationships. (Figs. 2, 3, and 6).

The third sound occurs during rapid ventricular filling, denoted by the decline of the V wave of the venous pulse. However, in our ex-

*The initial, coarser vibration of the first sound coincides with the sharp drop on the so-called A wave of the venous pulse, so clearly shown by lines *1* in Figs. 2, 3, and 5.

perience, it does not necessarily coincide with the end of rapid inflow, as shown in Fig. 1 and as claimed by Orías, et al. It may also occur midway on the downstroke of this wave (Fig. 5), or even near its summit (Fig. 3). In confirmation of the observations of Braun-Menéndez and Orías, it never bears any relation to the H wave, when this is present.

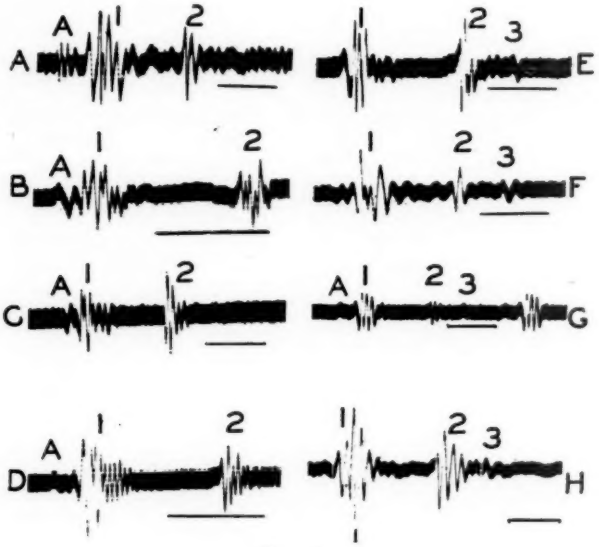

Fig. 7.

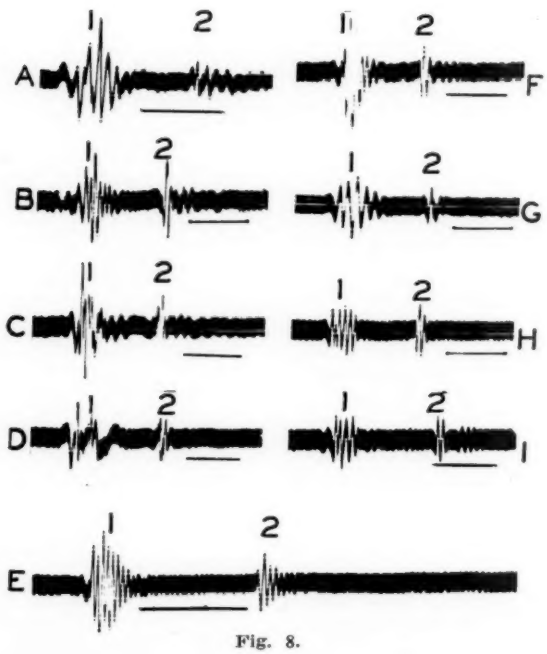

Fig. 8.

The question of whether or not this sound arises in the heart must be considered. It has apparently never been described in records taken directly from the dog's ventricle, nor is it present in sounds recorded from the esophagus (Taquini). Since the ribs, sternum, and, indeed, the whole body, as shown by ballistographic registration (Starr[14]), undergo brusque movements at this moment, the possibility that it originates in the chest wall, and, with some modes of registration, perhaps in the chest piece or recorder, should be considered. With our system of recording, these waves, because of their slow periods, could not have been of instrumental origin. However, when the chest was very lightly tapped by the finger while normal heart sounds were being recorded, similar and even more pronounced waves, with frequencies of 40 to 50/sec., appeared at various moments on the records. These facts and the irregular relation of the third sound to ventricular filling suggest that further evidence should be adduced that the third sound, whether recorded or heard, is caused by events actually occurring within the heart. Its accentuation, recognized as a protodiastolic gallop in some cardiac disorders, does not preclude such an origin, for it is conceivable that in such circumstances the movement of the heart and its relation to the chest wall may be altered.

CHARACTERISTICS OF SOUNDS RECORDED BY HIGH-FREQUENCY RECORDERS

Procedure.—Sounds from the region of the apex were recorded with capsules which had frequencies above 275/sec., with a projection distance of 5 meters. We followed the recommendations stated above, and from each person selected records which were as free from adventitious vibrations as possible, but were found, by comparison with other records, to contain nearly the full complement of vibrations for all sounds. Such records were obtained from 150 medical students, approximately one-half from sitting and one-half from recumbent persons.

Description.—In following our description of records, it must be kept in mind that the sound characteristics vary in the same person, and that several different types may occur in the same subject. Statements of the frequency with which certain types are found refer solely to the dominant types in any person. To aid in description of sound characteristics, a number of phonocardiograms are combined in Figs. 7, 8, and 9 in such a way that the attention of the reader may be focussed on a particular sound group. Obviously, each record illustrates features of other sound groups as well.

Types of atrial sounds are illustrated in Fig. 7 *A, B, C,* and *D*. This sound is usually composed of from 1.5 to 3 small vibrations, generally confluent with those of the first sound and rarely separated from it, as in curve *A*. Sounds of larger amplitude, or with more numerous vibrations, were never encountered. The duration was rarely longer

than from 0.04 to 0.06 sec., and the periods most commonly fall between 12 and 36 msec. (frequency, ca. 28/83 sec.). (See also Fig. 10.) Definite evidence of such presystolic or atrial sounds was obtained in 22 per cent of the persons who were studied while they were sitting, and in 27 per cent of those studied while they were recumbent.

Types of third sounds are shown in Fig. 7 *E*, *F*, *G*, and *H*. These were discovered in 4 per cent of the records made with the subjects sitting, and in 26 per cent of those who were studied while they were in the recumbent position. The third sound invariably consists of from 1 to 3 very small oscillations, begins from 0.10 to 0.14 sec. after the onset of the second sound, and lasts from 0.03 to 0.06 sec. As shown by plots of Fig. 10, vibrations with periods of from 20 to 30 msec. dominate, i.e., the calculated frequencies range from 33 to 50/sec.

The first sounds illustrated in Fig. 8 present a variety of groupings and conformations, a description of which presents a real challenge to one's command of the language.

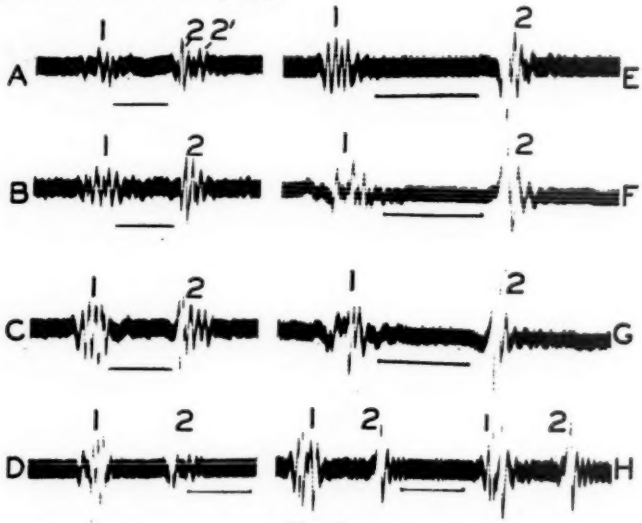

Fig. 9.

They are composed of a variable number of vibrations, most commonly 5 to 12. As shown in Fig. 10, their periods have a considerable range, but generally they fall between 9 and 30 msec., i.e., the calculated frequencies range from 33 to 111/sec. These frequencies correspond with those of previous calculations of Wiggers and Dean[6] (38 to 150/sec.), and with those of Williams and Dodge[15] (50 to 150/sec.), but are higher than the values given by Orías and Braun-Menéndez,[12] who calculated maximal frequencies of 55/sec. from records taken by low-frequency capsules. The durations also vary, but when all vibrations are recorded they are rarely less than 0.06 sec., nor more than 0.11 sec.

In going over all of our records, we found that, as regards configuration, they can be classified roughly in four categories:

Type I (Fig. 8 A and B).—These sounds are characterized by a crescendo-decrescendo series of vibrations, differing grossly as to individual periods, reaching a maximum about the beginning of ejection, and starting to undergo decrement during the early ejection phase. This type of first sound was described by Einthoven as characteristic of first sounds. It occurred in 26 per cent of normal males who were examined while they were in the sitting position, and in 37 per cent of a group of subjects who were studied while they were lying down.

Type II (Fig. 8 C and D).—These sounds are characterized by a similar series of crescendo-decrescendo vibrations of differing periods, but with a definite break of smaller vibrations near the middle, which suggests a double causation, one occurring during isometric contraction, the other during early ejection (see also Fig. 5). Sometimes they resemble the double grouping noted by Wiggers and Dean[6] in records taken directly from the exposed aortas of dogs. Orías and his various colleagues have stressed the frequent occurrence and importance of such groupings in human phonocardiograms. Clear-cut evidence of such division was certainly not present in over 15 per cent of our subjects.

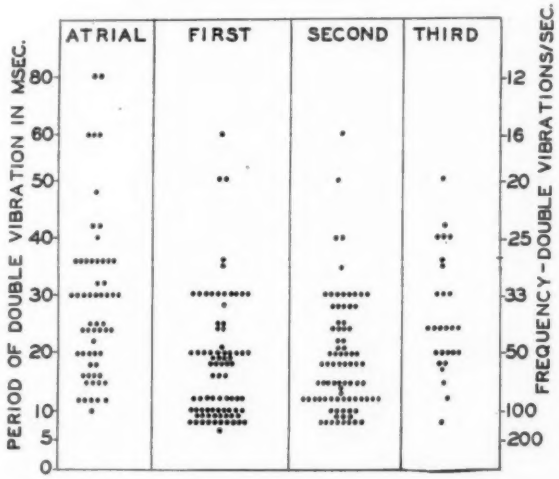

Fig. 10.—Plot showing distribution of frequency of four sounds analyzed in fifty records.

Type III (Fig. 8 E and F).—These sounds are characterized by a series of vibrations with comparative equality in periods of vibrations. As a rule, they increase rapidly to a maximal size and then decrease regularly, much as a set of free vibrations does. In these records, also, the second sound often showed similar characteristics. This suggests that there may be a resonating factor in chest walls. This type was found in 24 per cent of our subjects.

Type IV (Fig. 8 G, H, and I).—These sounds are characterized by a series of coarser and relatively smaller vibrations which almost immediately reach a maximum, maintain this maximum, and stop abruptly. Such vibrations were dominant, or occurred frequently, during inspiration in 35 per cent of our subjects. It is our impression that they may occur in conditions in which not all vibrations generated by the heart are transmitted to the chest wall.

The second sound generally consists of three or four rapidly decrescent vibrations of equal periods, lasting from 0.04 to 0.06 sec. Such typical complexes are shown in the curves of Fig. 8 *F, H,* and *I*. They were found in 72 per cent of our subjects. The rest exhibited various types of complexes, not generally described in normal people, and therefore illustrated in greater detail in Fig. 9.

In 8 per cent of our cases the second sound was prolonged (0.11 sec., or more), displayed irregular or bizarre forms, or showed a tendency to duplication (Fig. 9 *A, B, C,* and *D*). In 20 per cent of young men with normal blood pressures, the second sound at the apex was definitely accentuated; four examples of this are shown in Fig. 9 *E, F, G,* and *H*. This high incidence of accentuation of the second sound at the apex was surprising.

The range in frequencies of vibrations of the second sound is shown in Fig. 10. The dominant periods range from 8 to 30 msec., and their calculated frequencies from 33 to 111/sec., or exactly those of the first sound. These higher frequencies contrast with the ranges of 30 to 43 reported by Orías and Braun-Menéndez, who used low-frequency capsules.

SUMMARY AND CONCLUSIONS

1. The technical developments leading to more accurate registration of heart sounds by direct methods are discussed, and it is pointed out that many principles and deductions apply equally to the use of electrophonic methods.

2. Changes in the methods for direct sound registration originally suggested by Wiggers and Dean have proceeded in two opposite directions, viz., (a) changes which have increased the inherent frequency and damping of membranes, with reduction in their sensitivity and elimination of extraneous chest noises in the intervals between sounds (our laboratory), and (b) changes producing increased sensitivity of membranes, reduction in damping, and decrease in frequency to as low as 17/sec.

3. Phonocardiograms were recorded with both methods in conjunction with venous pulse tracings in order to study their relative practical merits and demerits. The conclusion was reached that, with proper precautions, systems with frequencies no greater than 30/sec. are capable of registering normal sounds and of recording them on top

of other noises in distinguishable fashion. Such sounds are correctly related to cardiodynamic events.

4. Systems with a higher frequency have the advantage that they can be so used that periods between groups of sound vibrations are silent, or nearly so, thus avoiding confusion in interpreting abnormal sounds and murmurs, and guaranteeing that the vibrations present are actually created by the heart. Such records give evidence of four sounds in persons in whom they can be demonstrated by more sensitive systems. However, the number and amplitude of vibrations are less than in records taken with more sensitive capsules, and the danger always exists that some vibrations belonging to different sounds are not recorded. This also applies to electrophonic records in which straight lines occur between sounds. In short, one procedure tends to record too much; the other, too little.

Overfiltration must be avoided, regardless of the recorder used. In our opinion, it is safer to err by introducing a few extraneous chest noises than by eliminating vibrations which are a part of the heart sounds.

5. The time relations of the atrial sound to the A wave preclude the possibility that it originates in contractions of atrial muscle or events immediately associated with it. The irregular relation of the third sound to ventricular filling and the fact that it cannot be recorded directly from the heart make it necessary to consider the possibility that its origin is thoracic rather than cardiac.

6. The characteristics of the four heart sounds and their incidence in 150 normal males are analyzed. Atrial sounds, consisting of a few, very small vibrations, were found in 22 per cent of our seated and 27 per cent of our recumbent subjects. The first ventricular sounds vary considerably in configuration and duration, but can be divided roughly into four types; these types are amply illustrated and described. Typical, short, second sounds, such as are commonly described, were found in 72 per cent of normal young males. Irregular, bizarre, prolonged, or reduplicated second sounds occurred in 8 per cent, and accentuated second sounds were found in 28 per cent of normal males. The third sound was present in 4 per cent of subjects when they were seated, and in 26 per cent of those who were lying down.

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THE MODE OF DEVELOPMENT OF COLLATERAL VENOUS CIRCULATION IN THE EXTREMITIES

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IMPAIRMENT of the venous circulation of the extremities may be just as disabling as impairment of the arterial circulation. It subjects the limbs to complications such as edema, varicosities, thrombophlebitis, stasis dermatitis, ulcerations, lymphangiitis, and cellulitis. The end results of venous obstruction depend upon how much collateral circulation develops. Much has been learned about the formation of arterial collaterals, and, recently, important methods of aiding in the development of these vessels have been devised. Little attention has been paid, however, to the mode of development of venous collaterals after obstruction of the large veins of the extremities.

In the past six years, at Charity Hospital, in New Orleans, and Gallinger Municipal Hospital, in Washington, I have had the opportunity to study a large number of cases of obstruction of the main venous trunks of the upper and lower extremities. In this group there were cases of acute thrombophlebitis, traumatic thrombosis, mechanical occlusion resulting from pressure by tumors, and, finally, occlusion caused by ligature. In this study I have been particularly concerned with the physiologic changes produced by the obstruction, the manner in which the collaterals developed, and the end results of the venous obstruction.

Occlusion of the main venous channels of an extremity produces changes in the local venous, arterial, lymphatic, and tissue fluid circulation. The degree of alteration of the circulation depends upon several factors. Acute obstruction is followed by more profound changes than gradual obliteration. True thrombophlebitis causes a more widespread disturbance than simple mechanical occlusion. In the main, however, the alterations that occur in the extremity following venous obstruction depend upon the size of the veins involved, the level of occlusion, and the number of tributaries obstructed. Adjacent tributaries are able to compensate promptly for obstruction of small veins, and there are no obvious ill effects. Ligation of the axillary vein at a single point may not produce signs of venous obstruction. Ligation of the femoral vein distal to the saphenofemoral junction does not produce edema, but if it is ligated above this point, edema will follow.

If the venous obstruction is acute, and, particularly, if it is caused by an inflammatory condition, there is an associated arterial spasm. This may be quite marked, and may even simulate acute thrombosis or em-

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bolism. During the period of spasm the extremity will show color changes, such as primary blanching, followed by cyanosis, and there will be a fall in the local temperature. The arterial spasm is usually of short duration, but may be intermittent. In a recent case of femoro-iliac thrombophlebitis which occurred in the puerperal period, the patient had several attacks of blanching of the affected extremity, accompanied by intense pain, and followed by cyanosis of the toes and foot. In one such attack the spasm was so marked and simulated arterial occlusion so closely that I explored the femoral vessels. The femoral artery was found to be about one-third the normal size, but still pulsated throughout its course. After stripping this vessel the pulse became larger, and the cyanosis disappeared promptly and did not return. The arterial spasm may therefore involve the main arterial trunks, as well as small branches and arterioles.

The first change that occurs in the venous system is an elevation of the local venous pressure, which in our series of cases has ranged from 170 to 1400 mm. of saline. This is followed rapidly by edema or infiltration of fluid into the tissues. The normal venous pressure in the arm at the level of the heart ranges up to 12 cm. of water. Krogh et al.[1] found that in normal subjects fluid was filtered into the tissues of the forearm when the venous pressure exceeded 15 cm. of water. Above an average venous pressure of 17 cm. of water the rate of filtration was directly proportional to the increase in pressure. We have found in patients that the amount of edema follows closely the degree of elevation of the local venous pressure. The pressure may be elevated sufficiently to cause fluid to filter into the tissue, but not enough to produce actual edema. We have designated this degree of increased pressure as the "sub-edema level," and for that stage at which the edema becomes obvious we have used the term "edema level." In the cases in which there is an elevation of venous pressure only to the sub-edema level, it has been shown that there is a definite elevation of tissue fluid pressure. The work of Burch and Sodeman[2] has thrown considerable light on this subject. They found that the tissue fluid pressure is a more sensitive indicator than venous pressure. In cases in which the venous pressure was elevated, but was not sufficiently high to produce edema, there were some escape of fluid into the tissues and an increase in tissue fluid pressure. As long as the venous pressure remains at or above the edema level, there is clinical evidence of edema.

Following occlusion of the large veins, collateral channels develop, and these, and the adjacent tributaries, attempt to compensate for the obstruction. As the obstruction is circumvented by collaterals, there should be a fall in the venous pressure and disappearance of the edema. This is not always the case because of two factors. First, the collaterals do not afford an adequate outlet for the venous blood, and the pressure remains at, or above, the edema level. Second, the collaterals may

be adequate only when the extremity is at rest and at the level of the heart. The venous pressure may be normal or at a sub-edema level under these conditions, and edema therefore disappears. However, with prolonged exercise, or when the limb is allowed to hang in a dependent position for a long period, edema reappears. In investigating these phenomena, several interesting facts have been found. As is well known, during active exercise there is a tremendous increase in the volume of blood flow to an extremity. When the venous system is intact, the exercise, although bringing this increased amount of blood to the extremity, does not produce an abnormal rise of venous pressure, for the competent veins readily carry away the added amount of blood. In other words, the balance between arterial inflow and venous output is maintained. In cases of venous obstruction this balance is upset. There is the usual increase in arterial inflow during the exercise, but, because of the obstruction, the venous outflow cannot keep pace with the intake, and there is an increase in the venous pressure. If this pressure is maintained for more than a few minutes, there is a prompt filtration of fluid into the tissues.

The following case illustrates the tremendous effect that exercise may have on venous pressure when the collaterals are inadequate. A colored woman had a radical, left-sided mastectomy performed in December, 1936, because of adenocarcinoma. About one month following the amputation she noticed that her left arm and hand became swollen during the day and that the swelling receded at night. She also noted that using the arm made the swelling more marked. This condition persisted, and she sought medical care. On admission to the hospital it was found that the left axillary vein was obstructed by scar tissue. On placing the arm at rest and elevating it above the level of the heart, the edema was markedly reduced within twenty-four hours. The venous pressure on the affected side was 160 mm. of saline, and on the normal side, 90 mm. Exercise, such as simply closing and opening the hand about 40 times per minute, caused the venous pressure on the obstructed side to become rapidly elevated. In one minute it was 400 mm., and at the end of three minutes it had reached 820 mm. and was still rising. The test had to be concluded because the apparatus would not permit a higher reading. After stopping the exercise there was a rapid decline in the pressure, so that at the end of 90 seconds it had again reached the stationary level of 160 mm. of saline (Fig. 1). On the normal side there was not more than a 10 mm. change in the venous pressure with the same exercise test.

Following the rise of venous pressure and the development of edema, changes take place in the lymphatic circulation. McMaster[3] has shown that when there is cardiac edema of the extremities, the lymphatic vessels are dilated, the valves are incompetent, and the lymph circulation becomes quite sluggish or ceases entirely. We believe that the same condition prevails in cases of edema of the extremities caused by local

venous obstruction. If the local venous pressure is elevated only to the sub-edema level, the lymphatics remain competent and carry away the excess fluid, thereby preventing sufficient accumulation to produce actual edema. When the venous pressure reaches the edema level, the lymphatic circulation fails, and edema becomes apparent.

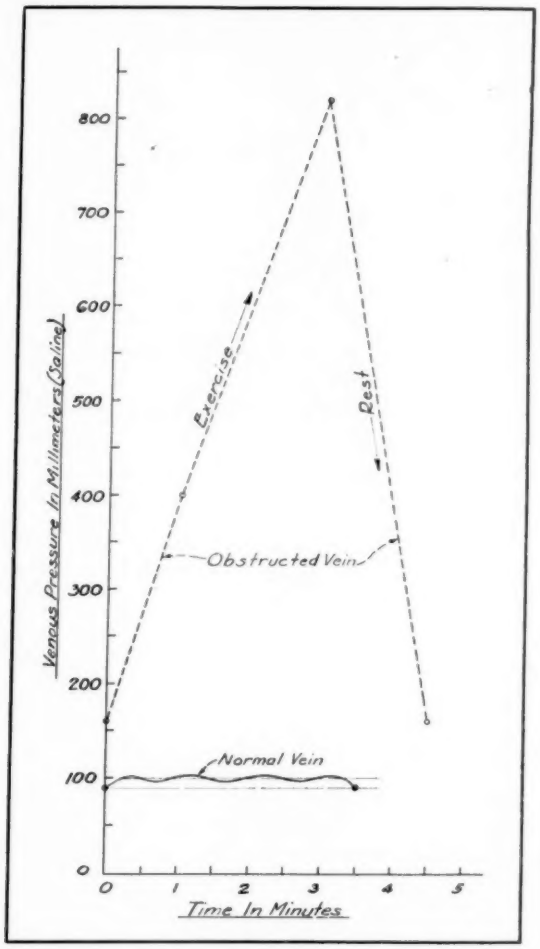

Fig. 1.—Chart showing effect of exercise on venous pressure in normal and obstructed veins. Note that pressure elevation in obstructed vein rises rapidly from 160 mm. to 820 mm. with three minutes of exercise. Note also the rapid return after stopping exercise. Note the slight variation in pressure in the normal veins under same exercise test.

Together with these physiologic alterations, certain structural changes take place in the venous system of the extremity after obstruction of the main trunks. By means of venograms we have been able to visualize practically the entire venous system of the upper arm and shoulder region. A special two-way syringe outfit was used in making the venograms, so that the cephalic and the basilic veins could be injected simultaneously. In this way a true picture is obtained of all of the main

vessels, showing the distribution, size, and normal contour, with the valves intact. As there is no obstruction or reversal of blood flow in the normal subject, the tributaries are not visualized (Fig. 2). In the cases of obstruction, the venograms not only visualize the main trunks up to the point of occlusion, but the communicating veins, the tribu-

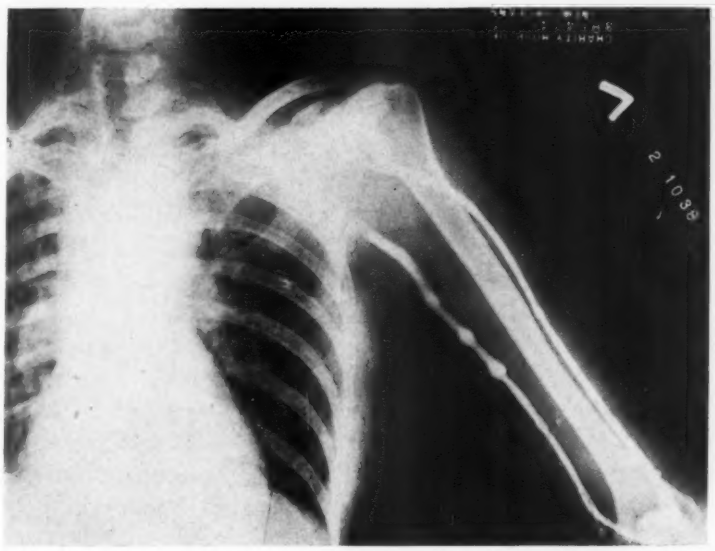

Fig. 2.—A normal venogram, made by injecting the basilic and cephalic simultaneously with a two-way syringe. Note the intact valves and absence of collaterals and tributaries.

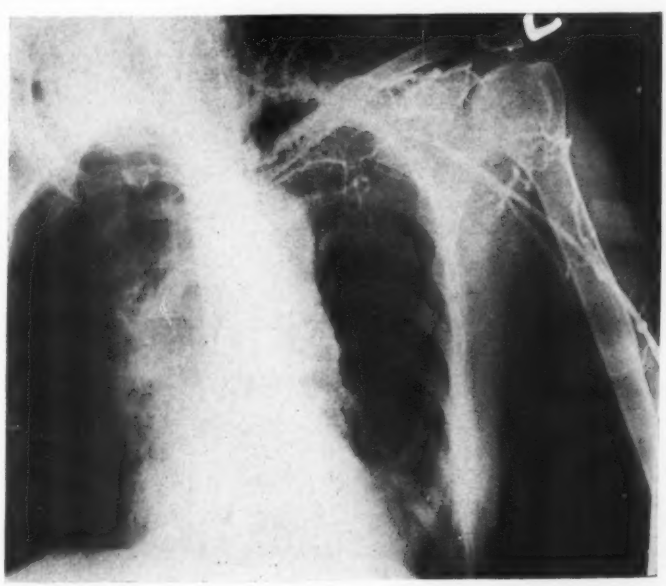

Fig. 3.—Complete obstruction of basilic, axillary, and subclavian veins. Tremendous development of collateral vessels over shoulder, upper chest, and neck. Note the tortuous, irregular course and distribution of the collaterals.

taries, and the collateral vessels, as well (Fig. 3). By this method we have made a study of some sixty patients who had varying degrees of venous obstruction. In this series of cases we have visualized the collaterals at all stages of their development, as early as the first forty-eight hours, and as late as twenty-two years, following the obstruction. We have, therefore, had the opportunity to view the progress of collateral formation and to observe the manner in which it develops.

Sabin,[4] in her excellent studies, showed that embryonic veins grow by budding from the parent stem. At first, solid strands of mesothelial cells extend out from the venous trunk. The solid strands then form a lumen and assume the function of a vein. This work was done on embryonic vessels. Does this same process take place in *mature vessels?*

The first structural change that occurs after obstruction of the main venous trunk is dilatation of this vessel distal to the point of occlusion. The valves fail to close completely, and blood is shunted through the communicating veins into the more superficial companion trunks, such as the cephalic when the axillary and subclavian veins are occluded, and the great saphenous when the femoral and iliac veins are involved. These companion veins dilate, and their valves become incompetent. If this fails to compensate for the obstruction, there is a reversal of blood flow into the tributaries, and they become dilated, tortuous, and elongated. Their branches, in turn, become enlarged, and there is a reversal of flow into these small veins. These new outlets form anastomoses with veins above the obstructed area. Often, long and tortuous courses are formed in an effort to provide an outlet for this venous blood which is under the abnormally high pressure. For instance, the long thoracic vein may shunt the blood into the intercostals and acromiothoracic veins, then into the internal mammaries. Branches from the cephalic unite with the transverse cervical and external jugular, and may even shunt the blood up through the cerebral circulation or into the thyroid veins and then to the opposite side of the neck. In case of femoroiliac obstruction, the saphenous may anastomose with the circumflex branches, and these may divert the blood into the superficial epigastrics or even all the way up to the cephalics. All of these steps are apparently accomplished by a process of dilatation, elongation, anastomosis, and reversal of blood flow. The new collaterals are irregular in size, course, and distribution. In a few cases there was undoubtedly an attempt to form new veins by the actual outgrowth of branches from the mature vessels. This was a poor attempt, however, and played little, if any, part in actually bringing about relief from the obstruction (Fig. 4). These new outgrowths were usually small tufts of veins budding from the tip of the obstructed trunk. It seems that practically all of the collaterals are made up from the pre-existing veins and venules. Furthermore, practically all of these changes take

place in the superficial veins. The collateral channels develop along the lines of least resistance, which means in the soft and pliable superficial tissues. The tissue pressure in the deeper layers of the extremities is sufficiently high to discourage the formation of collaterals, and, as long as the superficial veins are allowed to remain open, there is little tendency to form new, deep connections or anastomoses. In fact, when deep veins are obstructed they have a tendency to grow much smaller as the collaterals develop into the main channels. This is a very important point, because the superficial vessels depend to a great extent on muscular action to propel the blood forward. This is particularly true when the valves are incompetent and the limb is dependent. The transverse diameters of the collateral vessels may be greater than that of the original venous bed, but may fail completely to overcome the obstruction because of the absence of valves and the superficial position and devious course of the new channels.

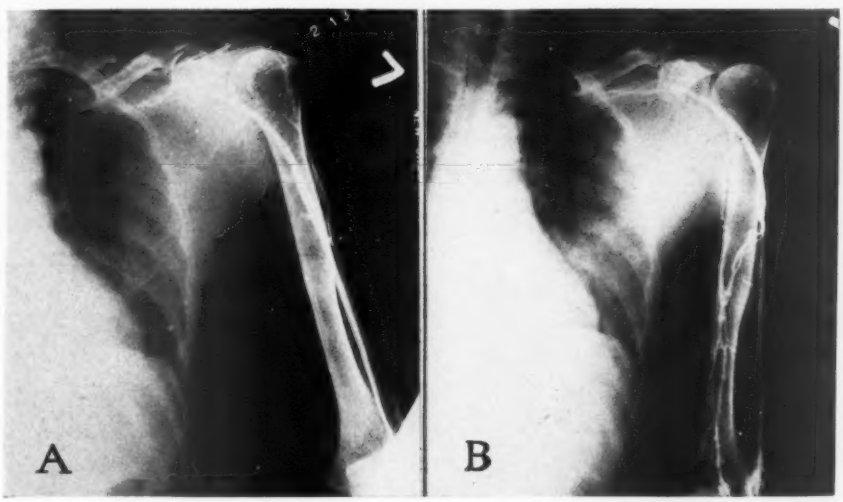

Fig. 4.—Occlusion of axillary vein by carcinoma of axillary lymph nodes. *A*, Venogram made by injection into cephalic. *B*, Injection made with two-way syringe. Note the newly-formed tuft of veins at point of obstruction of axillary veins.

The problem of abetting the formation of collateral venous circulation is far from solved, but it seems that any method, to be successful, must be designed to encourage the formation of deep collateral vessels. Recently we have been attempting to bring this about, after femoroiliac thrombosis, by obliterating the superficial veins immediately with an Unna's boot applied from the toes to the hip. This boot should be worn continuously for several months, until there has been a development of deep collaterals sufficient to compensate for the obstruction. Thus far, the results are encouraging. The boot tends to relieve the pain and lessen the edema. There is also evidence that it diminishes the arterial spasm by preventing loss of heat from the extremity. It is not necessary to keep the patient in bed; he is allowed to be up as

soon as the exciting cause of the thrombophlebitis, such as a surgical operation, will permit. By protecting the superficial venous circulation and encouraging the formation of deep collaterals, there is hope that the late sequelae may be prevented. In the deep collaterals, the normal muscular tone and the squeezing effect of muscular action will aid in propelling the blood toward the heart.

As a criterion of adequate collateral formation we have found that venous pressure measurements are most accurate. As long as the superficial venous pressure remains above the sub-edema level during rest, and if exercise causes a rise in pressure to the edema level, the collaterals are inadequate.

SUMMARY

Collateral veins develop from pre-existing veins and venules, but not by a simple mechanical process. The venous, arterial, lymphatic, and tissue fluid circulation are all involved. The main changes that occur in an extremity after obstruction of the large venous trunks are caused by the concomitant rise in the local venous pressure and the retardation of the venous blood flow. There is often an associated arterial spasm which may produce severe pain and other signs of impaired arterial circulation. The changes in the lymphatic and tissue fluid circulation are secondary to the increased venous pressure. The newly-developed collateral circulation often fails because of its structural deficiencies, its superficial position, and because of the long and devious course which it often pursues. Venographic studies and venous pressure measurements are of considerable value in ascertaining the degree and extent of the venous obstruction. Repeated venous pressure studies, made at rest and during active exercise, provide the most accurate criterion of the progress of the formation of collateral venous circulation in the extremities.

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THE CIRCULATORY EFFECTS PRODUCED IN A PATIENT WITH PNEUMOPERICARDIUM BY ARTIFICIALLY VARYING THE INTRAPERICARDIAL PRESSURE

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THE present understanding of the circulatory effects of pericardial effusion is based upon the work of Cohnheim.[1] He noted a rise in venous pressure and a fall in the arterial blood pressure when he increased the intrapericardial pressure by introducing oil into a dog's pericardium. This has since been confirmed by others on many different laboratory animals. In man, however, studies of the effects of increased intrapericardial pressure on the dynamics of the circulation have been limited to a few isolated observations. On two occasions, in the same patient, Stewart, Crane, and Deitrich[2] made simultaneous observations of the intrapericardial pressure and the venous pressure. They also demonstrated a reduction in the venous pressure and a proportional increase in the cardiac output following paracentesis of the pericardium. Caughey,[3] and others, likewise demonstrated a reduction in the venous pressure after pericardial paracentesis in cases of pericardial effusion. Zuccola[4] measured the reduction in intrapericardial pressure following pericardial paracentesis. We have had the opportunity of studying the effects of a sequence of changes in the intrapericardial pressure on the human circulation under conditions more readily controlled.

A twenty-year-old white woman was admitted to the University of Michigan Hospital in July, 1938, with tuberculous polyserositis. Therapeutic pneumopericardium and left-sided therapeutic pneumothorax were established. Following this she improved, and for three months prior to this study her condition was relatively stable. There was no dyspnea, cyanosis, or edema; the ascites, which was present on admission, disappeared after the establishment of the pneumopericardium and had not recurred. The liver, which had been considerably enlarged, became smaller, but could still be felt three fingerbreadths below the costal margin. The roentgenogram, which was taken twenty days before this study, showing the pneumopericardium and left-sided pneumothorax, is reproduced in Fig. 1. In the attempt to maintain a dry pneumopericardium, an opportunity was presented to establish the limits of pressure which would not unduly embarrass the circulation. Consequently, observations were made of the changes in pulse rate, respiratory rate, arterial pressure, venous pressure, and circulation time when the intrapericardial pressure was altered over a fairly large range by the injection of air.

METHODS

By fluoroscopic observation it was found that a needle could be introduced safely into the air-containing pericardial sac through the subxiphoid route with the patient in the supine position. With the needle in place, the intrapericardial pressure

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could then be varied by the introduction or removal of air by means of a pneumothorax apparatus. A Y tube from the needle permitted measurements of the intrapericardial pressure on a water manometer and simultaneous tambour recording on a kymograph of the pressure changes produced by the respiratory and cardiac cycles. The Erlanger apparatus was used to make a kymographic record of the pulse in the leg. The principle employed in the Erlanger apparatus was also used to maintain a relatively constant sensitivity of the tambour connected with the intrapericardial space throughout the period of observation. To accomplish this, a small balloon in a glass chamber, which could be adjusted to atmospheric pressure, was placed in the circuit, and this permitted changes in the intrapericardial pressure without changes in the recording level of the tambour. The pulse rate was also counted by palpating the radial artery. Arterial pressure was measured with a mercury manometer by palpation of the radial pulse, since the auscultatory method was not satisfactory in this patient. The respiratory rate was counted for periods of one minute and also recorded on the kymograph. The venous pressure measurements were made by the direct method, as modified by Lyons, Kennedy, and Burwell,[5] using the right antecubital vein. Circulation time was measured by the arm-to-tongue method, using decholin.

The intrapericardial pressure was increased in steplike fashion by the addition of air to the pericardial sac. After each change in pressure, time was allowed for apparent stabilization of the consequent circulatory changes.

It should be made clear that in this study the substance used to elevate the intrapericardial pressure was air. As air, in contradistinction to fluid, is easily compressible and has a lower viscosity, pneumopericardium and hydropericardium may well have different effects upon ventricular filling, even at the same pressure levels. The pressure relationships reported here, therefore, may not be directly transferable to pericardial effusion, but the direction of the changes will be the same.

At the time of these observations the patient suffered from some degree of impairment of cardiac function, as evidenced by the slightly elevated venous pressure, tachycardia, and hepatomegaly. The abnormally high intrapericardial pressure that was originally present had been somewhat reduced by the replacement of the effusion with air. Nevertheless, in order to maintain the pneumopericardium, the intrapericardial pressure had been kept above atmospheric pressure. Some impairment in cardiac function could therefore be expected, since Beck and Isaac[6] have demonstrated that merely exposing the heart to atmospheric pressure produces a diminution in cardiac output in dogs.

RESULTS AND DISCUSSION

The variations of venous pressure, pulse rate, arterial pressure, and circulation time with changes in the intrapericardial pressure are illustrated in Graph I. There were no significant changes in the rate or character of respiration throughout the entire period of observation, hence it is not included in the graph.

Intrapericardial Pressure.—On entering the pericardium, the pressure was found to fluctuate between +50 mm. of water during inspiration and +100 mm. during expiration. This was in accord with many previous observations on this patient. Table I shows the steplike changes in intrapericardial pressure, the amount of air added or removed to produce each change, and the inspiratory, expiratory, and mean intrapericardial pressure at each level. For convenience in discussing the

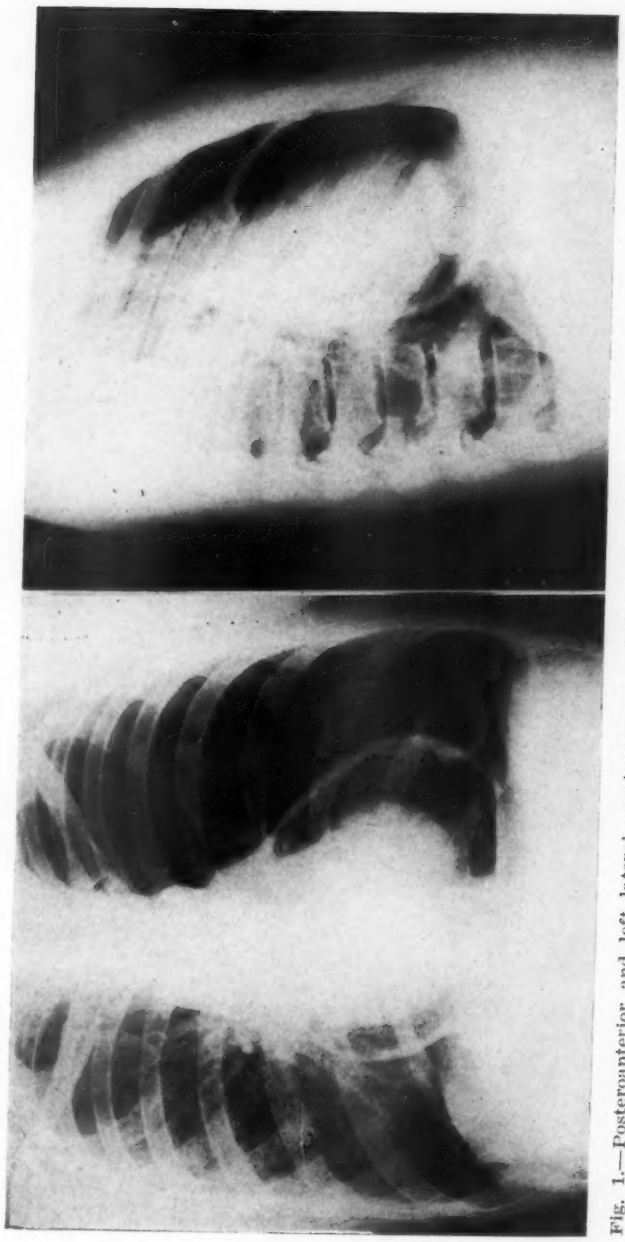
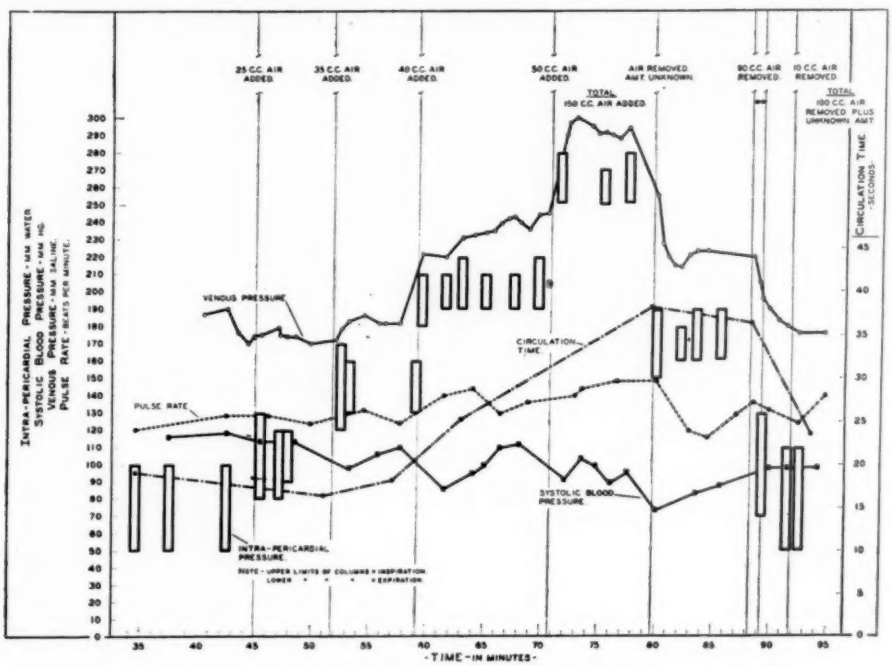


Fig. 1.—Posteroanterior and left lateral roentgenograms of the chest, taken seven months after admission to the hospital, four months after the establishment of pneumopericardium, and twenty days prior to the observations here reported.

various pressure levels hereafter, the mean intrapericardial pressure will be used.

Once a pressure level in the pericardium was established, it remained constant until altered by further addition or removal of air. There was no evidence of a change in pressure as a result of pericardial stretch, although this has been noted in experimental animals. The fluctuations in intrapericardial pressure caused by the heartbeat were too rapid to be measured on a water manometer, but they were well recorded on the kymograph (Fig. 2). The respiratory fluctuations in intrapericardial pressure, since they were slower, could be measured on a water manometer as well as recorded on the kymograph. Thus, a comparison of the recorded fluctuations caused by the heartbeat with those caused by respiration gave a rough index of the pressure changes within the pericardium produced by systole and diastole. As the intrapericardial pressure was increased, the changes in pressure caused by the heartbeat were less marked, suggesting that there was a decrease in diastolic filling.



Graph I.—Each measurement of intrapericardial pressure is represented by a rectangle which illustrates the range of pressure change caused by respiration. For the purpose of simplicity, the pulse rate and arterial pressure are placed on the same scale as intrapericardial pressure. This has the result of minimizing the graphic representation of the changes. The time, in minutes, is from the beginning of the observations.

As the intrapericardial pressure was increased, the fluctuations caused by respiration were decreased. Thus, with a mean intrapericardial pressure of 75 mm. of water the respiratory fluctuations were in the region of 50 mm., but at higher pressures these fluctuations were reduced to 25 mm. It seems possible in this case that the decrease of intra-

pericardial pressure accompanying inspiration facilitated diastolic filling of the heart. Thus, a reduction in the respiratory fluctuation of intrapericardial pressure may be a factor in determining the level of intrapericardial pressure at which severe tamponade will occur.

Venous Pressure.—It can be seen in Graph II that, at the beginning of the observations, the venous pressure was approximately 95 mm. of water above the mean intrapericardial pressure. Increasing intrapericardial pressure to 145 mm. did not affect the venous pressure appreciably. At this point, however, the difference between venous pressure and intrapericardial pressure was about 35 to 40 mm. of

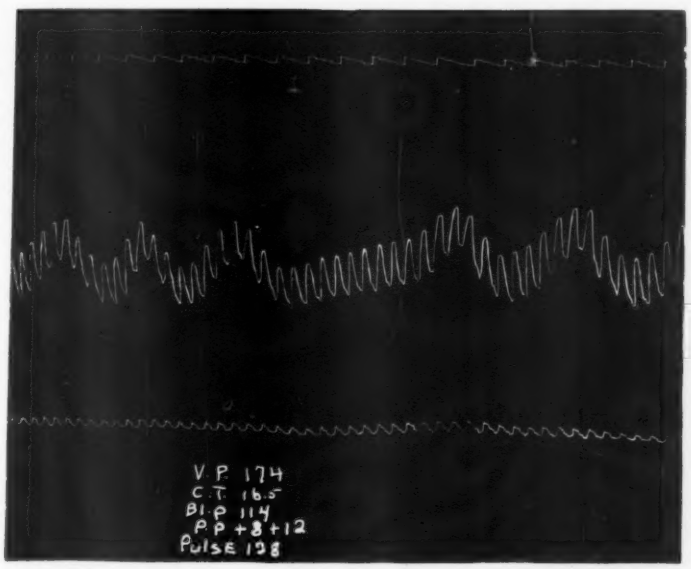


Fig. 2.—This section of tracing was taken between forty-five and forty-seven minutes after the beginning of the study. The center tracing shows the fluctuations in intrapericardial pressure with the respiratory and cardiac cycles. The lower tracing is of the arterial pulse, taken by means of the Erlanger apparatus. The upper tracing is time in seconds.

V.P. = venous pressure in mm. of saline.
C.T. = circulation time in seconds.
Bl.P. = systolic blood pressure in mm. of mercury.
P.P. = intrapericardial pressure in cm. of water.
Pulse = pulse rate in beats per minute.

water. A subsequent increase in intrapericardial pressure produced a proportionate increase in the venous pressure. With the final elevation of the intrapericardial pressure to 265 mm., the increase in venous pressure was not proportionate, and the difference between them fell to 25 mm. After about six minutes under these conditions, unequivocal signs of severe tamponade became evident. The patient appeared rather pale, there was cyanosis of the mucous membranes, and she became quite faint. The pulse became rapid and thready, and the arterial pressure fell. It appears plausible that in this case a venous pressure of 35 to 40 mm. above the pressure in the pericardium was necessary for the maintenance of an adequate circulation.

When the pericardial pressure was reduced by the rapid removal of air, the venous pressure fell, but remained 40 to 50 mm. above the intrapericardial pressure, and the symptoms of severe tamponade were quickly relieved. Further reduction in the intrapericardial pressure, to approximately its original level, was accompanied by a fall in venous pressure, also to its original level.

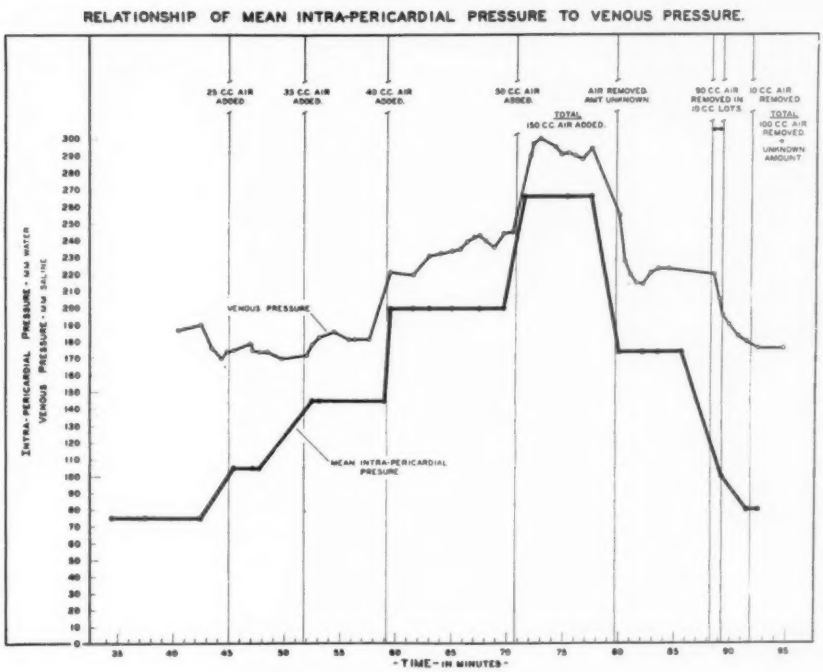
Circulation Time.—As is shown in Graph III, the circulation time increased from nineteen seconds to a maximum of thirty-eight seconds. As was noted with venous pressure measurements, no significant changes were manifest until the intrapericardial pressure was elevated above 145 mm. of water. This is better illustrated in Graph IV, in which the venous pressure and circulation time are plotted against the mean intrapericardial pressure.

Pulse Rate.—With each increase in the intrapericardial pressure there was an increase in the pulse rate, but the rate tended to return toward its original level after a few moments (Graph V). Like the venous pressure and circulation time, the pulse rate was not markedly affected until a mean intrapericardial pressure of 145 mm. of water was attained. With further increases in pressure there was a decided increase in pulse rate, reaching a maximum of 148. With the sudden release of pressure in the pericardium, just after the onset of severe tamponade, there was

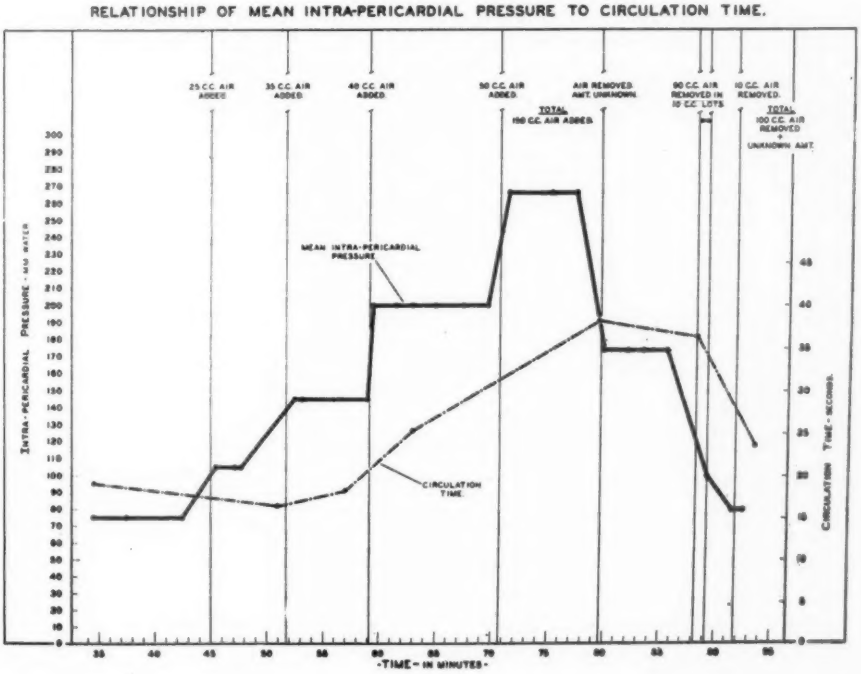
TABLE I

VOLUME AIR ADDED OR REMOVED (C.C.)	TOTAL AIR ADDED OR REMOVED (C.C.)	INTRAPERICARDIAL PRESSURE MM. WATER		
		EXPIRATORY	INSPIRATORY	MEAN
0	+ 0	+100 +100 +100	+ 50 + 50 + 50	+ 75
+25	+ 25	+130 +120 +120	+ 80 + 80 + 90	+105
+35	+ 60	+170 +160 +160	+120 +130 +130	+145
+40	+100	+210 +210 +220 +210 +210 +220	+180 +190 +190 +190 +190 +190	+200
+50	+150	+280 +275 +280	+255 +250 +255	+266
*Air removed. Amount unknown	?	+190 +185 +190 +190	+155 +160 +160 +165	+174
-90	-90, plus amount unknown	+130	+ 70	+100
-10	-100, plus amount unknown	+110 +110	+ 50 + 50	+ 80

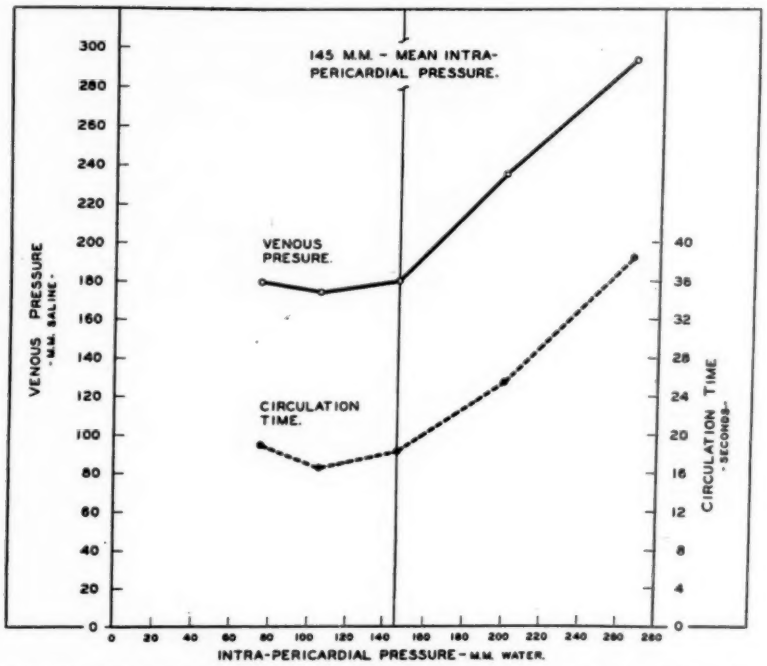
*Air released through stopcock—not measured.



Graph II.

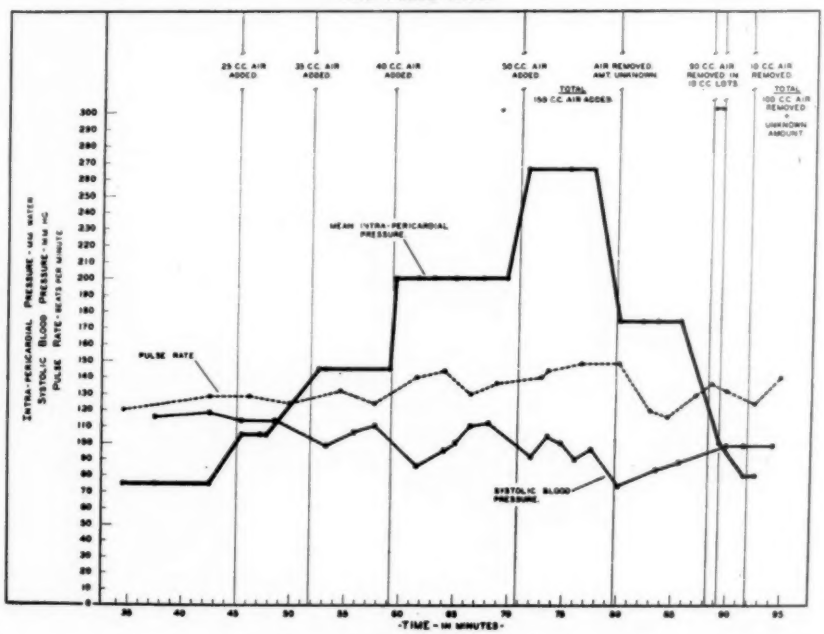


Graph III.



Graph IV.—The venous pressure in mm. of saline and the circulation time in seconds (ordinate) are plotted against the mean intrapericardial pressure in mm. of water (abscissa). It can be seen that no significant changes occur in either venous pressure or circulation time until the mean intrapericardial pressure is elevated above 145 mm. of water.

RELATIONSHIP OF MEAN INTRA-PERICARDIAL PRESSURE TO SYSTOLIC BLOOD PRESSURE AND PULSE RATE.



Graph V.—See legend to Graph I.

a striking but momentary fall in the pulse rate from 148 to 116, which was slightly below the original rate. This accompanied a rather prompt fall in the venous pressure and a diminution in the visible and palpable distention of the neck veins. This temporary fall in the pulse rate must, therefore, have coincided with a marked increase in the diastolic filling of the heart.

Arterial Pressure.—The arterial pressure tended to fall with each increase in intrapericardial pressure, and to return to its previous level in the next few moments. When the mean pressure in the pericardium was 266 mm. of water, the arterial pressure fell slowly throughout the six minutes of observation. The low level of 74 mm. of mercury was recorded coincident with the release of air from the pericardium.

SUMMARY

1. Observations on changes in pulse rate, respiratory rate, arterial pressure, venous pressure, and circulation time were made with artificially produced changes in intrapericardial pressure in a patient with pneumopericardium. These relationships have been illustrated graphically.

2. The intrapericardial pressure fluctuated with respiration, and, as higher pressures were reached, these fluctuations decreased.

3. The intrapericardial pressure fluctuated with systole and diastole. Kymographic tracings were made of the fluctuations in intrapericardial pressure caused by respiration and the heartbeat. With the higher intrapericardial pressures, the changes in pressure produced by systole and diastole were less marked.

4. Significant changes in pulse rate, arterial pressure, venous pressure, and circulation time did not occur until the intrapericardial pressure was elevated to, or above, 145 mm. of water.

5. In order to maintain the circulation, it was necessary that venous pressure exceed intrapericardial pressure by at least 35 to 40 mm. of water.

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COMPRESSION OF THE SUBCLAVIAN VEIN BY THE FIRST RIB AND CLAVICLE, WITH SPECIAL REFERENCE TO THE PROMINENCE OF CHEST VEINS AS A SIGN OF COLLATERAL CIRCULATION

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THE occurrence of prominent veins on the anterior surface of the chest wall is rather common. To our knowledge, no adequate explanation has been advanced for this phenomenon. Certain factors tending to cause prominence of the chest veins may be listed as follows:

1. Congenitally large or unusually numerous veins.
2. An increase in blood flow, as would occur with increased metabolism. Much use of the arm and chest muscles.
3. A transparent skin and a thin superficial layer of fat.
4. Increased pressure in the superior vena cava.
5. Arteriovenous anastomoses in the arms.

Since none of these factors seemed to account for the striking difference in prominence of veins among most individuals, we were required to seek another explanation. From study of certain extreme cases, one in particular (Case 128, reported below), the conclusion was reached that such dilatation of the chest veins usually indicates that a collateral venous system has developed. Presumably, these vessels are enlarged to aid the outflow of blood from the upper extremities when the subclavian vein has been partially obstructed between the first portion of the clavicle and the first rib, anterior to the scalenus tubercle.

The primary reasons why we believed that this mechanism was responsible for compression of the subclavian vein were:

1. When the shoulders were thrown back, the veins became more distended.
2. The veins were prominent in individuals whose shoulders were naturally in a relatively posterior position, and whose clavicles were therefore in an upward and backward position.
3. The veins were rarely prominent except in persons with broad and somewhat deep chests.

This condition, which may be termed a clavicle-first rib compression syndrome, should be distinguished from the so-called scalenus anticus or cervical rib syndrome, to which much attention has been devoted.

The history of the development of current knowledge of the cervical

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rib syndrome and of the similar, so-called scalenus anticus syndrome does not warrant extensive review. In the original article of Gruber,[1*] the later reports of Buzzard,[2] Bramwell,[3] Keen,[4] Jones,[5] Todd,[6] and Stiles,[7] and the more recent ones of Brickner and Milch,[8] Naffziger[9] and Ochsner and his associates,[10] the explanation given for the nervous and vascular changes in the arms in cases both of cervical rib and of high first rib has been pressure on, or stretching of, the subclavian artery and the brachial plexus behind the scalenus anticus muscle and over the first rib. In justification of this explanation is the fact that in numerous instances improvement has followed section of the insertion of the scalenus anticus muscle, or removal of the anterior portions of either cervical ribs or abnormal first ribs. Therefore, this syndrome is concerned with compression posterior and lateral to the scalenus tubercle. The fact that signs and symptoms develop late in life has been attributed largely to the natural drooping of the shoulders, which exerts increasing stretch on the brachial plexus. One of the diagnostic tests of this syndrome is the fact that temporary relief from pain is obtained when the patient voluntarily elevates the arm and shoulder.

The independence of the cervical rib or scalenus anticus syndrome from that described herein has been recognized by several observers who have seen cases in which the subclavian vein, lying anterior to the scalenus muscle, was not compressed. Likewise, we have observed four patients with cervical ribs who, in spite of characteristic nervous and arterial signs and symptoms, did not present unusually prominent chest veins. On the contrary, moving the shoulders upward and backward, displacing the clavicle backward against the first rib, increased the venous congestion by further obstructing the subclavian vein. Such upward motion of the shoulders, as stated above, relieved the tension on the subclavian artery and brachial plexus in the cervical rib-scalenus anticus syndrome, but, in the cases to be described, tended to compress further the subclavian artery as well as the vein.

SUPERFICIAL VENOUS PATTERN ON THE THORAX

In order to clarify the differential diagnosis of venous obstruction, and the formation of collateral channels on the chest wall, it is necessary to review the normal and abnormal patterns of the superficial veins.

It has long been known that the arrangement of the superficial veins on the surface of the thorax shows the most extreme variations. Whereas studies have been made on the arrangement of the superficial veins of the extremities,[11] and its variations in different races,[12] as far as we are aware, nothing has been attempted in the way of classifying patterns found on the trunk. This lack of recorded observation is no

*The first case reported (Clinical Records of *Lancet* 2: 633, 1860) was that of Dr. W. H. Willshire. The patient was observed at Charing Cross Hospital. It was recognized that he had supernumerary ribs, but no symptoms were evident.

doubt due to their inconstancy. However, the pattern can be shown to consist of certain fairly well-defined elements, and each of these elements exhibits, in turn, variations in its prominence from subject to subject (Fig. 1).

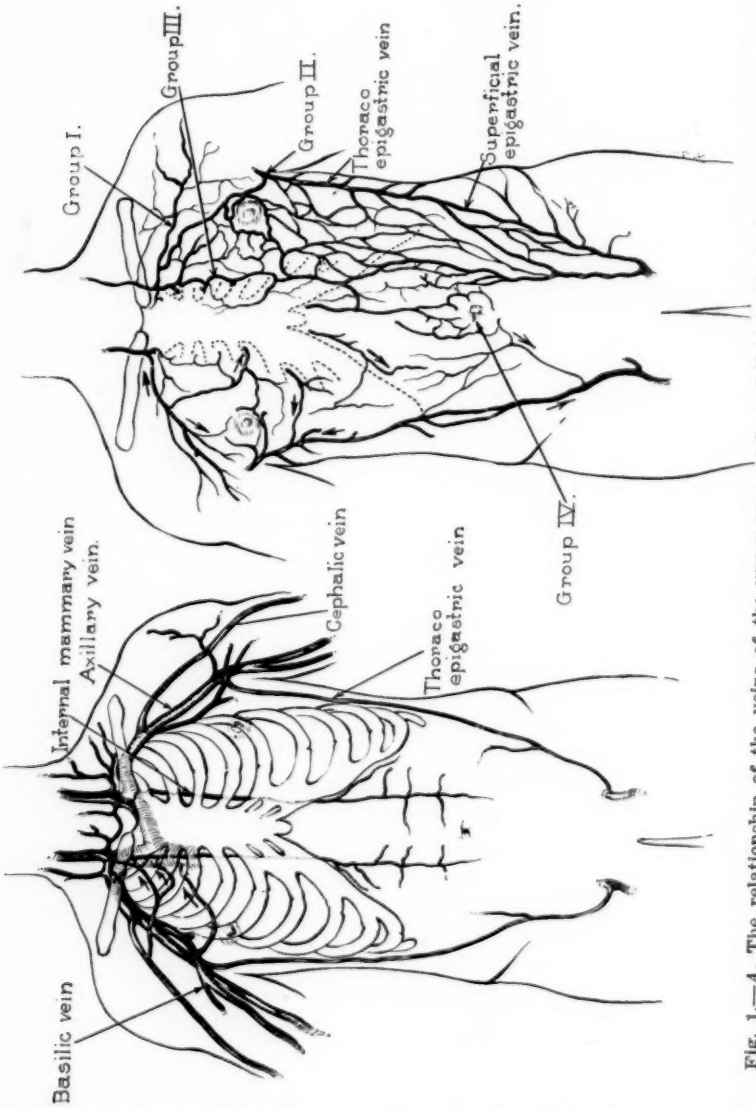


Fig. 1.—*A*, The relationship of the veins of the upper arm, neck, and thorax, illustrating the normal course and the collateral pathways commonly developed with obstruction of the subclavian vein. *B*, The pattern of the superficial veins of the anterior chest and adjacent regions.

The veins which make up this superficial pattern are essentially as follows:

1. In the upper part of the chest, a group of veins, plexiform in arrangement, can be traced from the cephalic vein, close to the point where it pierces the delto-pectoral triangle, passing superficially over the upper and lateral parts of the thorax, across the clavicle, to join

the external jugular vein. One of these veins is often well marked. The stem of this group may arise from the basilic vein or may be composed of veins derived from both the basilic and the cephalic veins. The relative constancy of this arrangement is explained by the fact that during embryologic life much of the blood from the developing upper limb bud is drained over the rudiment of the clavicle to the external jugular vein. The superficial veins are of the greatest importance at this period, and this group therefore represents the early primary pattern.

2. A second group of veins drains the venous plexuses about the nipple in both male and female subjects. This group follows, as one or more tributaries, the course of the external mammary artery, constituting its venae comites. They usually open into the basilic or axillary vein, occasionally into the cephalic or subclavian. This group of external mammary veins has usually free connections with the fairly constant thoraco-epigastric vein, with which it may be associated in a common trunk. The thoraco-epigastric trunk is found along the flanks, extending from the superficial epigastric veins of the inguinal region to the axilla.

3. A variable series of veins passes through the anterior parts of the intercostal spaces into the internal mammary veins. Those passing through the second and third, or third and fourth intercostal spaces are usually larger than the rest, particularly in the female subject. Freely anastomosing with one another, connecting vessels communicate above directly with the external jugular, or indirectly by means of the cephalic connection. In addition, insignificant vessels communicate across the midline with the veins of the opposite side.

4. Veins from the lower part of the chest wall drain downward and communicate through perforating twigs around the costal margin with the venae comites of the musculophrenic artery, with the superficial epigastric veins, and with deeper veins, particularly in the umbilical region (Fig. 2).

The pattern of the enlarged veins, presumably resulting from compression of the subclavian vein, and displayed in the cases herein considered, consisted, in general, of an exaggeration of the normal. (Fig. 3*A* and *B*.) It was most evident in the upper thorax. The veins of group I, passing from the cephalic to the external jugular vein, were unusually prominent, and the blood flow was consistently mediad and upward. Those of groups II and III participated in this engorgement, and the flow was toward the intercostal spaces. The veins of group IV were usually not enlarged. The presence of these veins obviously indicated the opening up of collateral pathways from the upper extremity by way of the cephalic and basilic to the internal mammary and external jugular veins.

Other pathologic conditions render these patterns most conspicuous, but the degree and extent of their prominence, together with the direction of blood flow, are usually distinctive. In obstruction of the superior vena cava, the engorgement of the veins over the trunk is not only more extreme, but also more generalized. The prominence of the superficial inferior epigastric and thoraco-epigastric veins, together with the downward direction of blood flow, is characteristic. An important diagnostic feature is the prominence of these veins as they pass from the jugular veins downward over the clavicles to the superficial thoracic plexuses. The flow in these veins is downward, in con-

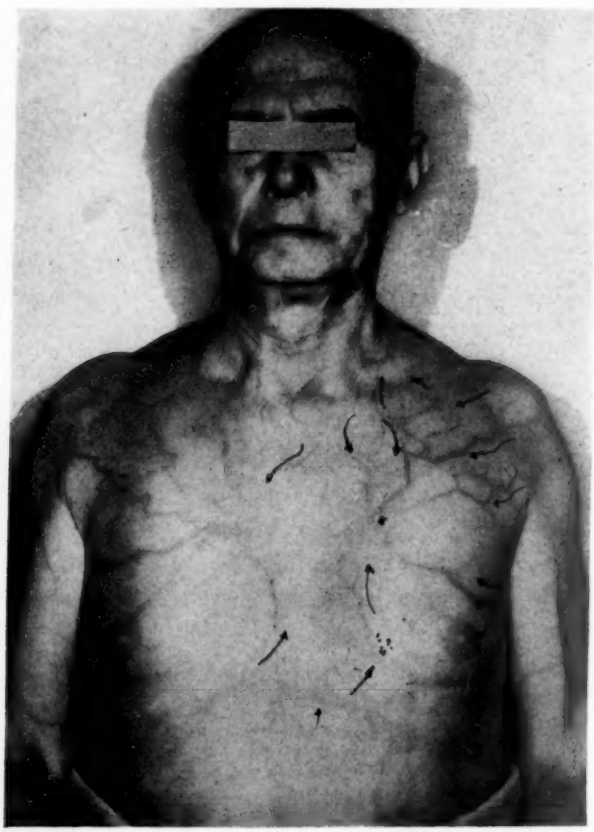
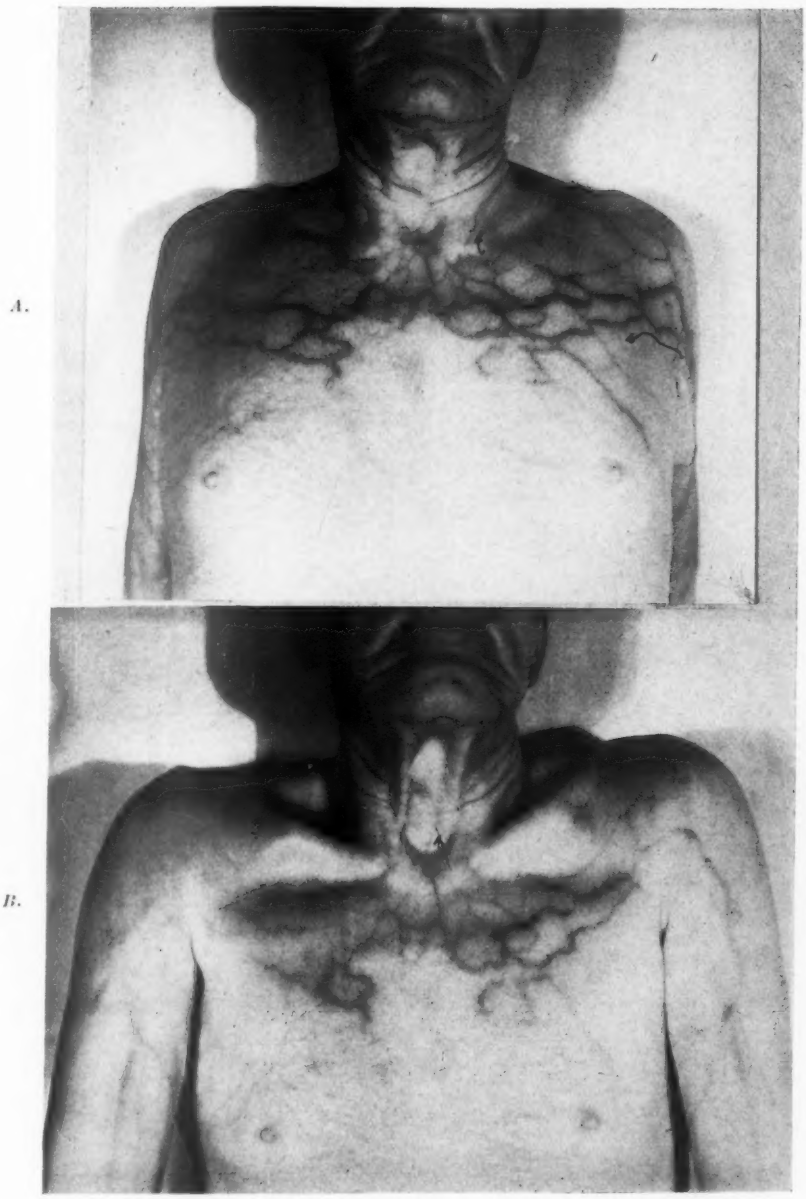


Fig. 2.—R. C., male, 70 years old. Infrared photographs, illustrating a somewhat exaggerated normal pattern.

trast to the commonly observed upward flow (Fig. 4). In a case of obstruction of the left innominate vein, the venous pattern was more prominent on the left, and the drainage for the most part was toward the right side. The veins of group I passed to the right to connect with, and drain into, the vessels of the supraclavicular region. The veins about the left breast crossed superficially over the sternum to



A.

B.

Fig. 3*A* and *B*.—Case 128. F. A., male, 72 years old. Extreme case of the syndrome of bilateral subclavian vein compression. Infrared photographs, illustrating the collateral venous supply from the cephalic and basilic veins in three major channels, communicating with the external jugular veins and with the internal mammary veins by means of the perforating veins in the first, second, third, and fourth intercostal spaces. Note that there is little engorgement of the lower chest veins, or crossing of venous plexuses over the midline. *A*, With shoulders thrown back. *B*, With shoulders thrown forward.

join the veins of group III on the opposite side, and, passing through the intercostal spaces of that side, apparently entered the right internal mammary veins. Those entering the second and third intercostal spaces on the right were especially prominent (Fig. 5).

The direction of blood flow in the surface veins of the thorax must be influenced by such valves as exist in these veins. From an exami-

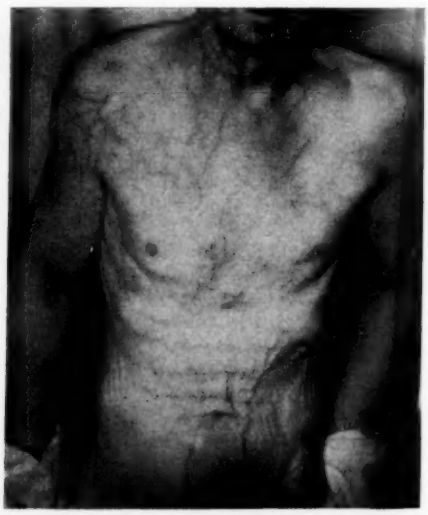


Fig. 4.—Male, 44 years old. Superior vena cava obstruction caused by mediastinal tumor. Infrared photograph, illustrating the downward direction of development of the collateral veins from the arms, as well as from the neck and superficial chest tissues.

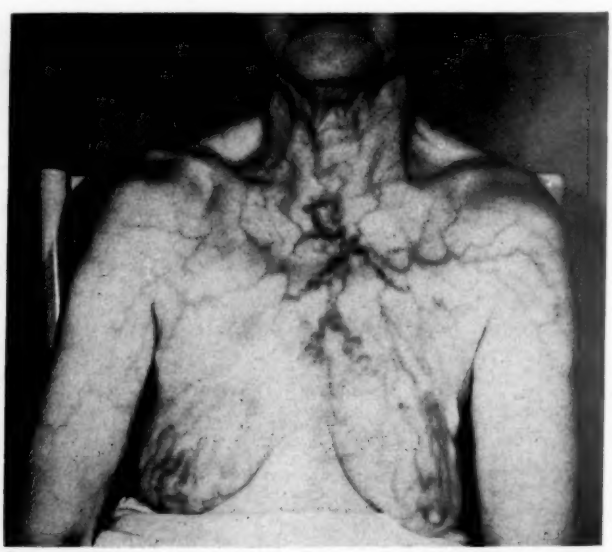


Fig. 5.—H. F., female, 65 years old. Aortic aneurysm, partially obstructing the left innominate vein. Infrared photograph, illustrating collateral veins draining the left superficial chest tissues, the left upper arm, and the left superficial neck tissues, by crossing to the right side. Note that the veins communicate with the right external jugular and right perforating anterior chest veins.

nation of several normal subjects, it would appear that the blood is drained predominantly in a medial direction. While a few radicles which drain the upper and outer portion of the thoracic wall appear to empty into the cephalic, the blood in the major vessels of group I passes over the clavicle to the supraclavicular and external jugular veins. The blood from the plexuses about the nipple appears to pass both medially and laterally through veins of groups II and III. The veins of group IV are rather difficult to discern during life unless the subject is very thin. The blood flow in the majority of the vessels of this group is upward toward the vessels of group III, but in a few veins it seems to be downward toward the abdominal plexuses.

In the later months of pregnancy, and during lactation, the venous plexuses of the chest wall are especially prominent and generally dilated.[13] The group III veins, passing to the intercostal spaces, are notably engorged, as are those of group I, but to a lesser degree. The deeper position of the external mammary veins makes their enlargement less conspicuous* (Fig. 6).

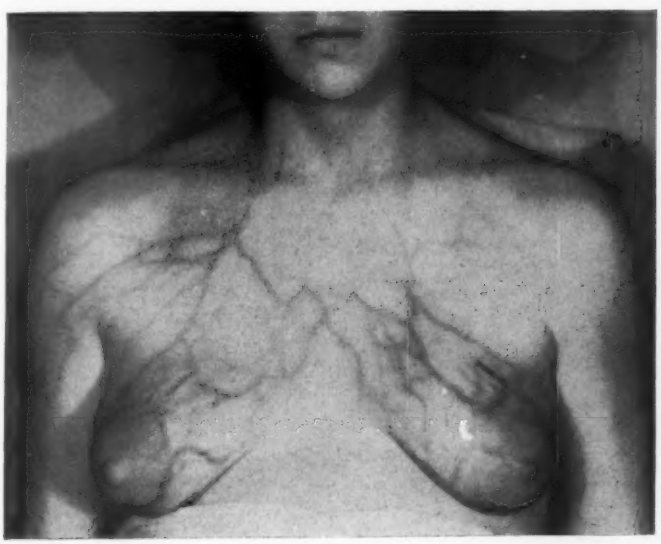


Fig. 6.—M. B., pregnant woman, 23 years old. Infrared photograph, illustrating distention and increased number of superficial chest veins draining lower chest during lactation.

In the syndrome that we describe, the pattern of group I stands out conspicuously in the upper thorax, and group II is likewise prominent, but to a lesser extent. The blood flow in this condition is very obviously centripetal.

Before proceeding to a discussion of the cases actually studied, it is necessary to discuss the relations of the subclavian vein and the possible mechanism of its obstruction (Fig. 7).

*Observations on venous distribution have been made by several individuals, particularly Loth[14] and Franklin.[15]

The subclavian vein, a direct continuation of the axillary, is described as commencing at the outer border of the first rib, and ending behind the medial end of the clavicle, where it joins the internal jugular to form the innominate. It receives, as a tributary, the external jugular vein. In its course it runs a little forward, as well as medially, anterior to and below the corresponding artery, from which it is separated by the scalenus anterior muscle. Slightly arched as it passes over the rib, it possesses a single bicuspid valve, placed a fraction of a centimeter lateral to the opening of the external jugular vein. The

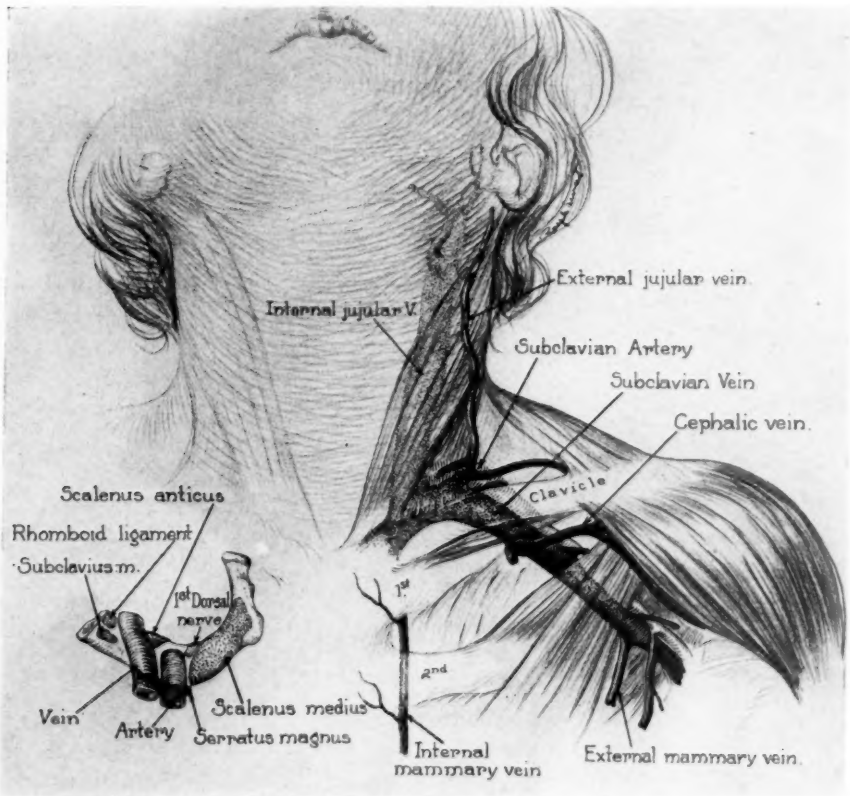


Fig. 7.—The relationship of the subclavian vein, subclavian artery, and adjacent structures.

space which it occupies between the scalenus anterior muscle and the clavicle is very narrow; in the adult its width is scarcely 1.5 cm. Resting on a rigid floor formed by the first rib, which it occasionally faintly grooves, the vein is held securely in position by fascia. This fascia, which is a portion of the so-called clavi-pectoral fascia, separates the vein anteriorly from the clavicle, subclavius muscle, and nerve, but, because it is attached to the clavicle, it binds the vein firmly to that bone. In consequence, movements of the clavicle are transmitted to

the vein, and it has long been recognized that forward movement of the arm holds it open.

It may be demonstrated that the clavicle, carrying with it the subclavian muscle, can, by pressure against the thoracic cage, totally occlude not only the vein, but also the subclavian artery. If the arm is carried behind the back and drawn downward and across to the opposite side, the radial pulse will disappear. Occlusion of the vessels is perhaps the result not only of clavicular pressure, but also, in part, of drawing the vessels, which are fixed proximally by the less resistant fascial sheath, over the rib. Such a mechanism of compression tends therefore to involve most readily the vein, less readily the artery, and least of all the trunks of the brachial plexus which lie behind the artery.

A summary of the factors tending to produce obstruction of the subclavian vein between the clavicle and the anterior portion of the first rib is as follows:

1. The first factor is the height of the first rib and the lateral projection of the arc of the rib. It is difficult to obtain information concerning these phenomena from clinical examination alone. It was stated arbitrarily that the patient had a broad upper chest when this structural characteristic was obvious. A roentgenologic examination was made in more than 75 per cent of the patients studied, and this kind of chest was found to occur especially in patients under 20 years of age who presented prominent anterior chest veins.

Unusual depth of the chest, as evidenced by increased length of the anteroposterior chord of the arc of the first rib, was apparently less likely to produce subclavian obstruction than was the lateral projection or width of the chest. In many cases in which the chest was of the "emphysematous" type, with increased depth, the chest veins were not prominent.

The increasing frequency of this phenomenon after the age of forty suggests, however, that either elevation of the ribs or their increased anterior projection—or perhaps both factors—must contribute to the venous obstruction. It is recognized that increasing age would tend to make the development of a collateral venous circulation more apparent because of the long duration of the process. Which of these three factors, appearing with increasing age, is of greatest importance cannot be stated at present. Changes in the thoracic index (transverse chest diameter in cm., times 100/ sagittal chest diameter) with increasing age have been measured by Martin,[16] Hösch-Ernst,[17] Bach,[18] and others. It is agreed that the width increases in proportion to the depth from birth to approximately the age of 16 years, and that the depth increases steadily in proportion to the width from the age of 21 years through the remainder of life.

2. The second factor of importance is the position of the clavicle, especially its angle above the horizontal plane of the sternoclavicular joint, and back of the frontal plane of that joint. The factors governing the position of the clavicle, other than the height of the sternoclavicular joint and the depth of the chest (the anteroposterior chord of the arc of the first rib), are: (a) the length of the clavicle and its curvature, of which the latter is not commonly reported as having great variations; and, especially, (b) the anteroposterior position of the shoulder (the acromioclavicular joint). Backward position of the shoulders, as in a so-called "good posture," was generally found in conjunction with a broad upper chest and well-defined collateral chest veins.

3. The third factor of importance is high thoracic kyphosis, which tends to throw the shoulders forward, freeing the clavicles of the ribs. A slouched posture, with low shoulders, will accomplish this same change in relation of the clavicle and ribs, and will prevent encroachment on the narrowed subclavian space which would otherwise be produced by broad ribs or backward slope of the clavicles. A lower thoracic kyphosis, or other causes of postural, anterior tilt of the trunk, may produce an apparent anterior thrust of the shoulders without actually changing the anteroposterior relation of the shoulders to the frontal plane of the chest. Thus, in certain patients, a slouched posture may maintain the mechanical relations responsible for obstruction of the subclavian vein.

4. The fourth factor, which is extremely difficult to evaluate in individual cases, is the pressure exerted by soft tissues. The subclavius muscle may be developed to an unusual degree, and thereby increase obstruction of the subclavicular space. Likewise, in certain instances, supporting straps for brassieres, or trouser suspenders, may press on the trapezius muscle and indirectly transmit pressure to the deeper tissue of the supraclavicular triangle. Such an instance was demonstrated in Case 118, in which slight edema of the right arm developed, apparently from partial obstruction of the subclavian vein, and was relieved by loosening the brassiere supporting straps (Fig. 12).

Increased bulk of the scalenus anticus muscle could hardly exert pressure anteriorly on the subclavian vein. However, as has been suggested by Craig and Knepper,[19] and others, increased activity of this muscle may be a factor in elevating the anterior end of the first rib.

5. It is well known that thoracic scoliosis thrusts the ribs laterally and upward on the same side of the body as the convexity of the scoliosis. Scoliosis of appreciable degree was found in eighteen of the 132 patients studied, and marked asymmetry of development of the chest veins was observed in all but two of these patients (Fig. 12). In four of these patients, veins were prominent on only one side of the chest.

6. Increased venous pressure in the superior vena cava might be thought to cause prominence of chest veins. However, we do not believe that this explanation is adequate, because in our series of cases no instance of concomitant distention of the jugular veins was observed.

NOTE.—Two patients were observed who did not show marked collateral venous circulation in the chest wall but did present unusual distention of the left external jugular veins during all of the respiratory cycle save a short portion of the inspiratory phase. It is our belief that these are cases of partial compression of the external jugular vein, prior to its junction with the subclavian vein, by the head of the clavicle at the sternoclavicular joint and an upward sloping first rib.

CASE REPORT

The mechanisms involved and the clinical observations in a well-marked case of subclavian vein obstruction may be illustrated by the following case report.

A man, 72 years of age (Case 128), entered the University of California Hospital Outpatient Department complaining of cough. He had been a sailor until the age of 50 years and had spent many hours pacing the deck with his arms behind his lower back. For approximately ten years he had been subject to frequent "chest colds," which resulted in a moderately productive cough lasting for periods of two to six weeks. For the preceding six or seven years he had noted progressive dyspnea on exertion, but this discomfort had never become severe enough to incapacitate him for such activity as slowly climbing a flight of stairs. He was troubled also by a dull, aching pain in the left shoulder region caused by motion of that joint. There were no pains or paresthesias in the lower arms or hands, although the hands tended to become unusually cold and bluish in cool weather.

Physical examination revealed an average degree of generalized arteriosclerosis, a ruddy facial complexion, and an erect posture, with the shoulders held high and backward even when the body was relaxed. No scoliosis was present. The blood pressure (brachial) generally ranged from 160/96 to 186/110 mm. Hg.

The chest was both deep and broad, and the lungs were hyperresonant to percussion; the breath sounds were normal except that expiration was somewhat prolonged and low-pitched over the bases of the lungs. The clavicles were directed upward and backward at an angle of 28° above the horizontal plane (26° as measured on the roentgenogram of the chest).

There was no distention of the jugular veins, but the superficial veins of the arms and hands were unusually prominent. Traversing the chest horizontally on either side there were three, distended, major veins which formed a plexus with smaller veins in certain areas. The upper of these three veins on each side was a continuation of the cephalic vein of the upper arm; it crossed the anterior portion of the deltoid muscle, then progressed mediad and cephalad toward the midline (Fig. 3). The second vein appeared on the chest from the upper portion of the axilla and advanced horizontally toward the midline, dividing and disappearing through perforating veins in the first, second, and third intercostal spaces near the sternum. The third vein appeared still lower, around the fold of the pectoralis major muscle, and passed mediad across the breast above the nipple, paralleling the second vein; after intercommunication with other superficial veins, it disappeared in the second, third, and fourth intercostal spaces near the sternum.

The effect of voluntarily throwing the shoulders forward was to collapse these distended veins (Fig. 3*A* and *B*). With the patient in a reclining position and the left arm vein held at a fixed level 6 cm. posterior to the anterior surface of the chest,

the venous pressure in the left median cephalic vein by direct manometer measurement was 12 cm. of water with the shoulders thrown forward, and 16.5 cm. of water with the shoulders held backward in their customary position.

The arm-to-tongue circulation rate, as determined by injection of sodium dehydrocholate (technique of Winternitz[20]), was 14 seconds with the shoulders thrown forward, and 17.5 seconds with the shoulders held backward.

These three phenomena indicated that there was venous obstruction in the normal axillary and subclavian channels. Further evidence of obstruction distal to the axillary vein was obtained by visualization of the venous channels by injecting Diodrast (modified technique of Wohlleben[21] and others) into the median cephalic vein in the antecubital fold. Two cubic centimeters of Diodrast were injected by means of a Luer syringe and a 16-gauge needle in a period of two seconds, then 5 c.c. in approximately one second, and then 3 c.c. in a period of three seconds, at the expiration of which time roentgenograms were obtained.

Figs. 8 and 9 were made within twenty minutes of each other, using the same vein and with the patient in approximately the same reclining position; Fig. 8 was made when the shoulders were thrown forward, and Fig. 9 when they were held backward. It is apparent from inspection of these roentgenograms that, with the shoulders held forward, the blood from the arm veins, especially the cephalic, followed the normal course, entering the axillary vein below the clavicle, where dilution of the opaque substance by blood from the deep veins rendered it transparent to the roentgen rays. Little of the blood was carried through the superficial collateral veins, and one may readily assume that the deep channel from the axillary vein to the superior vena cava was functionally unobstructed.

On inspection of Fig. 9, it is observed that little radiopaque blood entered the normal channel of the axillary vein, but passed through the superficial collateral veins, seen on the surface of the chest, and either entered the perforating veins of the median chest wall to be diluted by blood from the internal mammary veins, or partially crossed the clavicle to enter tributaries of the jugular veins medial to the termination of the subclavian vein in the superior vena cava. Under these circumstances, the blood in that portion of the cephalic vein communicating between the superficial tissues and the axillary vein would be relatively stagnant, as likewise would be the blood in the axillary and major portions of the subclavian vein. These observations leave little doubt that, under the circumstances stated, obstruction of the subclavian vein is brought about by the mechanism previously suggested.

With this patient in his normal posture, evidence of obstruction of the subclavian artery was afforded by a constantly present, rough, systolic murmur and systolic thrill, which were noted on both sides over the axillary artery, immediately below its emergence beneath the lateral portion of the clavicle. Both murmurs disappeared when the shoulders were thrown forward. As further proof of arterial compression, when the shoulders were held forward the arterial blood pressure in both arms increased, although only slightly, from 172/102 to 178/110. Oscillographic records were obtained, but were not remarkable. These phenomena occurred not uncommonly in patients presenting this syndrome, but, except in two doubtful cases, no harmful effects could be attributed to the arterial compression.

DISCUSSION OF CASES

All of the individuals studied were grouped according to the degree of venous engorgement on the chest, as follows: normal, questionable, moderate, and marked. In Table I, only moderate and marked groups were included (see Table II, also).

In this study, the shapes of the chests were classified as: broad upper chest, deep chest, average chest, and narrow chest. The clavicular angles were measured above the horizontal in the frontal plane. They were classified as 0 to 10°, 10 to 20°, 20 to 30°, and over 30°. (For consideration in Tables I and II, the patients were divided into those having, or not having, broad chests, and into those with vertical clavicular angles above 20°, or below 20°, upward from the horizontal plane.)

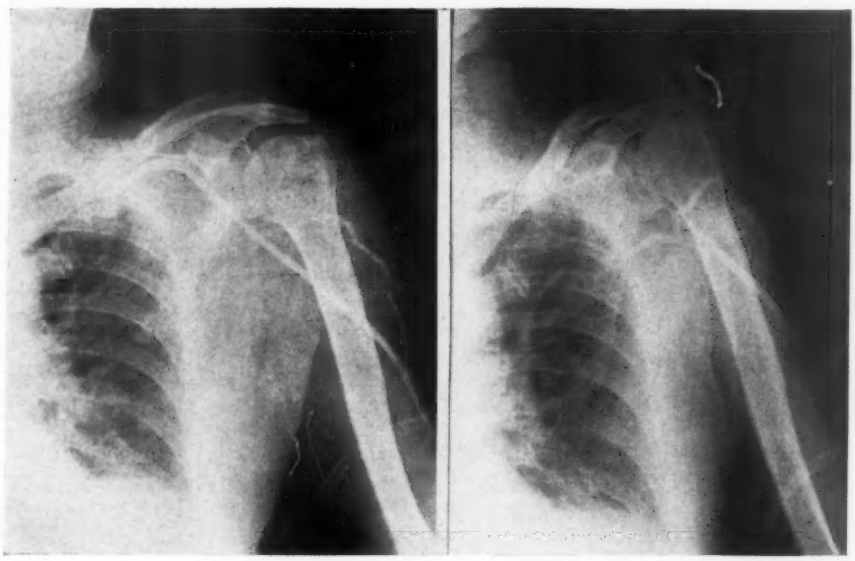


Fig. 8. Fig. 9.

Fig. 8.—Case 128. Patient holding shoulder forward. Roentgenogram of left upper arm and shoulder and upper chest region after injection of Diodrast into left median cephalic vein. Illustrates the normal pathway of blood from the cephalic vein into the axillary vein. Note the relative paucity of blood flow in the superficial chest veins.

Fig. 9.—Case 128. Similar to Fig. 8, except that the shoulder is held backward. Note the absence of blood in the communicating vein between the cephalic and axillary veins, and the heavy blood flow in the collateral veins in the superficial chest tissues.

An attempt was made to measure clinically, in all cases, the upward and backward angles of projection of the clavicles. Motion of the clavicle generally takes place almost equally upward and backward with backward motion of the shoulders. The vector of both the horizontal and vertical planes seemed to be indicated by measurement of the vertical angle alone, without measurement of the horizontal. Therefore, only the vertical angle of deviation is given in the table of measurements (Table I). In most of the cases in which there were very prominent chest veins, this vertical angle exceeded 35° above the horizontal plane.

Measurements of the clavicular angles made from routine roentgenograms were extremely unsatisfactory because, when roentgeno-

grams of the chest are made, the patient is generally ordered to throw his shoulders forward. Fig. 10 (Case 128) illustrates the clavicles in three positions which were obtained by normal and altered postures of the shoulders. In the roentgenograms taken without distortion of posture, the ratio between the distance along a horizontal plane from the midline of the body to the farthest lateral projection of the first rib, and the costo-acromial joint distance, generally exceeded 1:2 in cases of obstruction of the subclavian vein. This ratio emphasizes the apparent shortening of the clavicle which projects backward and upward, and also the increased lateral projection of the first rib. These measurements were recorded on the roentgenograms of a child, 5 years of age, with unusually prominent chest veins, and, as can be seen from the illustration, with high, laterally projecting ribs (Fig. 11).

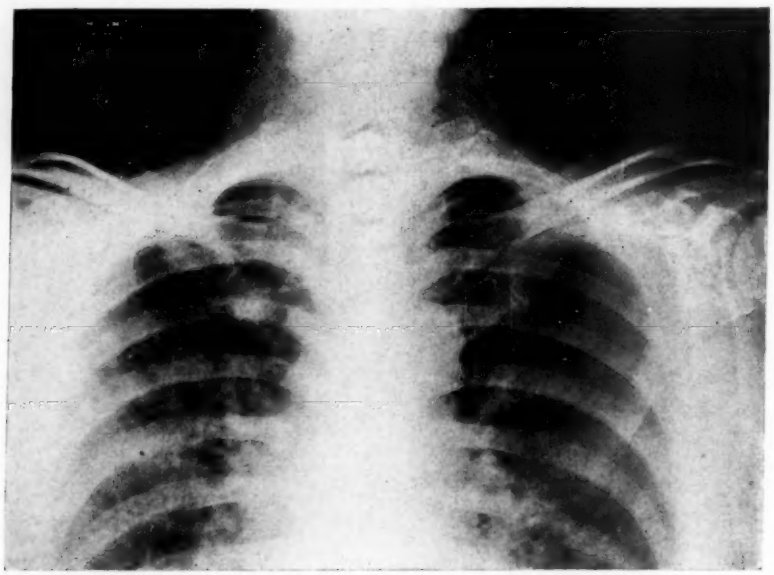


Fig. 10.—Roentgenogram of the chest with the shoulders (a) in normal position, (b) thrust forward, and (c) held backward. Illustrates the depression and elevation of the clavicles in the latter two positions when contrasted with the normal mid-position. Note the high, broad sweep of the first rib, as well as the elevated angle of the clavicle, even in the mid-position.

In consideration of the results summarized in Table I, it will be observed that the percentage of individuals showing marked development of chest veins increases from 12 per cent under the age of 30 years, to 50 per cent over the age of 60 years. The incidence for the entire group was 29 per cent. As has been mentioned previously, the tendency toward flattening and elevation of the ribs, as well as toward an increase in the anteroposterior diameter of the chest, may account for the increasing incidence that occurs with advancing age. Likewise, the longer duration of the process would allow more time for development of the collateral circulation.

There was no appreciable difference in the incidence according to sex; 28 per cent of the patients were men, and 30 per cent were women. If permanent distention of chest veins after lactation were a factor in producing the type of prominent chest veins under discussion, we would expect a greater incidence in women than was actually found.

In examining column III and column IV of Table I, it will be observed that in over 80 per cent of the patients with prominent chest veins the clavicular angle was high; and, likewise, that in over 80 per cent of the patients the upper chest was broad. This was true of almost all of the younger patients who had prominent chest veins, in most of whom the depth of the chest was not increased. Not a single instance was observed in which both characteristics were absent, and there was only one case in which one was absent and the presence of the other was questionable.

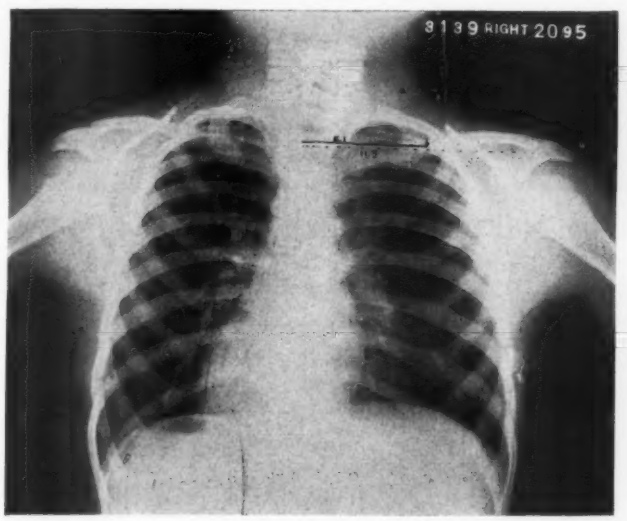


Fig. 11.—Male, 5 years old. Roentgenogram, illustrating broad chest, with high, laterally projecting upper ribs, in a child with prominent chest veins.

In contrasting the clavicular angle and configuration of the chest in those who did not have prominent chest veins, one observes that a fairly high percentage of this group showed characteristics that should tend to produce obstruction of the subclavian vein (56 per cent of the former, and 32 per cent of the latter). Three of this group showed both characteristics to a pronounced degree. In one case (No. 109, a man 30 years of age), the absence of prominent chest veins could not be explained by the data obtained from his physical examination; but the two other patients had marked upper thoracic kyphosis. The presence of high thoracic kyphosis, or a slouched posture, has been mentioned as a factor tending to throw the shoulders forward, even though holding them in a relatively high position. Such a position would

TABLE I

STUDY OF CHARACTERISTICS OF PATIENTS WITH DISTENTION OF CHEST VEINS

(124 UNSELECTED INDIVIDUALS OF VARIOUS AGES)

AGE GROUP	I		II		III		IV		V	
	CASES IN EACH DECADE		CASES OF VENOUS DISTENTION		CASES OF VENOUS DISTENTION WITH CLAVICULAR ANGLE OVER 20°		CASES OF VENOUS DISTENTION WITH BROAD UPPER CHEST		CASES OF VENOUS DISTENTION WITH POOR POSTURE	
	NO.	PER CENT OF TOTAL	NO.	PER CENT OF GROUP	NO.	PER CENT OF COL. II	NO.	PER CENT OF COL. II	NO.	PER CENT OF COL. II
Under 10 yr	7	6 } 33	2	29 } 13	2	100 } 80	2	100 } 80	0	
10 to 19 yr.	23	18+	2	9	1	50	1	50	0	
20 to 29 yr.	9	9+	1	9	1	100	1	100	0	
30 to 39 yr.	8	6	2	25	2	100	1	50	0	
40 to 49 yr.	18	14	5	28	5	100	5	100	0	
50 to 59 yr.	27	21+	9	33	8	89	8	89	2	22
Over 60 yr.	32	25	16	50	14	87	13	81	2	12.5
Totals	124	100	37	30	33	89	31	84	4	11

Males: 71 cases (57.5 per cent); females: 53 cases (42.5 per cent).

TABLE II

STUDY OF CHARACTERISTICS OF PATIENTS WITHOUT DISTENTION OF CHEST VEINS

(124 UNSELECTED INDIVIDUALS OF VARIOUS AGES)

AGE GROUP	I		II		III		IV		V	
	CASES IN EACH DECADE		PATIENTS WITHOUT VENOUS DISTENTION		PATIENTS WITHOUT VENOUS DISTENTION WITH CLAVICULAR ANGLE OVER 20°		PATIENTS WITHOUT VENOUS DISTENTION WITH BROAD UPPER CHEST		PATIENTS WITHOUT VENOUS DISTENTION WITH POOR POSTURE	
	NO.	PER CENT OF TOTAL	NO.	PER CENT OF GROUP	NO.	PER CENT OF COL. II	NO.	PER CENT OF COL. II	NO.	PER CENT OF COL. II
Under 10 yr.	7	6 } 33	5	71 } 87	2	40 } 50	1	20 } 31	0	9 } 10
10 to 19 yr.	23	18+	21	91	11	53	7	33	2	
20 to 29 yr.	9	9+	8	91	4	50	4	50	2	25
30 to 39 yr.	8	6	6	75	3	50	3	50	2	33
40 to 49 yr.	18	14	13	72	7	54	5	38	4	31
50 to 59 yr.	27	21+	18	67	13	72	6	33	4	22
Over 60 yr.	32	25	16	50	9	56	2	12.5	8	50
Totals	124	100	87	70	49	56	28	32	22	25

Males: 71 cases (57.5 per cent); females: 53 cases (42.5 per cent).

maintain the clavicles in an abnormally anterior position, and therefore away from the first ribs. The incidence of high thoracic kyphosis and slouched posture is entered in column V of Tables I and II. It will be seen that both were uncommon (11 per cent) in patients with venous distention, in comparison with those without venous distention (25 per cent). There were no patients under 50 years of age who had venous distention and a definitely slouched posture.

Certain explanations may be offered for some apparent discrepancies, namely, why not all patients with subclavian vein obstruction showed the supposedly characteristic forms of clavicle and chest, and why some individuals with these forms did not show evidence of venous obstruction.

In the first place, the degrees of compression exerted by the rib and clavicle may vary independently of one another. To be specific, (1) both may contribute to compression; (2) one may produce constriction while that caused by the other is of only minimal importance; and, (3) whereas one may apparently be in a position to produce constriction, the other may, because it occupies a normal or even a counteracting position, be far enough away to prevent actual constriction.

In the second place, the shoulders may be farther forward or backward on the median frontal plane of the chest than the vertical inclination of the clavicle would indicate. This would be the case especially when a longer kyphosis had shifted the axis of the chest forward, so that the shoulders would occupy a position relatively anterior to the general body axis, but relatively posterior to the frontal chest plane. The influence of faulty posture in increasing the costal-subclavicular space must be evaluated from this standpoint before any importance can be assigned to it.

In the third place, it must be acknowledged that the assignment of a characteristic shape to the chest, for the purpose of classification, is arbitrary and liable to error. Likewise, measurements of the clavicular angles were checked in only a few cases by roentgenographic examination with the patient in a natural posture, and this might also introduce error. In measuring such angles clinically, it is assumed that the position of the clavicle is the one normally maintained by the individual throughout daily life, but this may not necessarily have been the case.

Last, and most important, is the fact that the veins may vary in prominence because of any of the other reasons mentioned previously, and not on account of obstruction of the subclavian vein.

Roentgenographic examinations generally confirmed the clinical impressions, but certain characteristics of the first rib, such as its thickness and minor changes in its configuration in the critical anterior portion, have not as yet been studied roentgenologically. It is hoped

that more exact criteria will be developed by further, detailed study of the roentgenograms.

Because of the change in the relation of structures which occurs after death, we have not found it possible to draw conclusions from measurements of variations in the subclavicular spaces in cadavers presenting either prominent or normal chest veins. The degree of transparency of the skin and the depth of the subcutaneous fatty layer may alter the appearance of superficial chest veins.

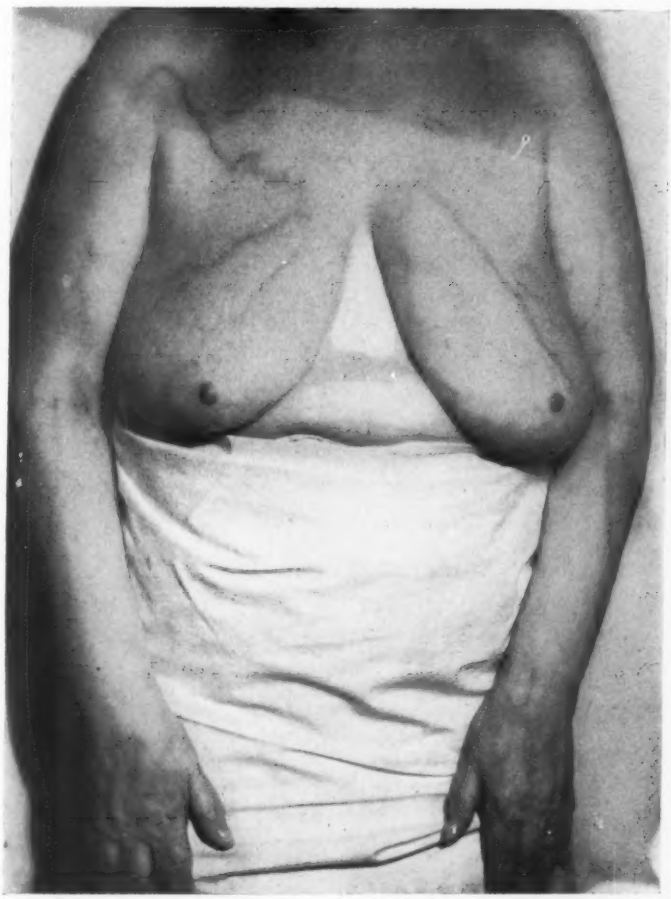


Fig. 12.—Case 118. G. M., female, 62 years old. Slightly obese patient, with moderate, right, thoracic scoliosis, and heavy, pendulous breasts. Illustrates the greater development of collateral veins on the right side of the chest. Note that the pull of the breasts has deflected the large upper chest veins downward. Furrows in the soft tissues of the shoulders where pressure of the brassiere straps occurred, may be seen. There is slight edema of the right lower arm.

Pressure of the clavicle on the subclavian artery as it crosses the first rib does not seem to be of appreciable importance. In many of the cases in which there was presumptive evidence of obstruction of the subclavian vein, a rough systolic murmur was noted when the

chest piece of the stethoscope was placed over the subclavian or axillary artery below the lateral third of the clavicle. In most cases, a systolic thrill was felt, also; and both thrill and murmur disappeared when the patient's shoulders were voluntarily thrust forward. This act obviously released compression on the subclavian arteries. As has been mentioned previously, this forward motion of the shoulders caused partial collapse of the superficial chest veins in the patients who had the syndrome under discussion, presumably because it enabled venous blood from the arms to flow through the larger, deep channels of the axillary and subclavian veins.

Only two patients (Case 127, a woman 44 years old, and Case 53, a man 53 years of age) had symptoms suggesting the possibility of artery or nerve involvement, namely, numbness and slight aching in both arms. In both cases, these symptoms were of varying degree throughout the day, becoming more severe toward evening, and disappearing when the patient rested in a reclining position. The former patient had had symptoms for approximately six months, and the latter for about two years. No muscular atrophies, gangrene of the skin, or other unusual changes were observed in their arms or hands.

In many of the patients, when the shoulders were thrust forward, the systolic blood pressure in both arms increased as much as 8 to 20 mm. Hg. In Case 53, the blood pressure was 86/54 in the normal posture, and 104/56 when the shoulders and clavicles were thrown forward. It seems probable that compression of the subclavian artery by the clavicle may account for some of the commonly observed differences of blood pressure in the two arms of certain patients, whether or not they have obstruction of the subclavian vein. These differences were observed in four cases in this series, in three of which there was obvious scoliosis, although one of the patients had no prominence of the chest veins. This patient (Case 123) was a woman, 28 years old, who presented a slight left thoracic scoliosis. Her blood pressure was 104/56 in the right arm, and 86/50 in the left arm. When her shoulders were thrust forward, the blood pressure of the right arm remained approximately unchanged, but that in the left arm rose to 106/60.

NOTE.—There have been many reports of unexplained thrombosis of the axillary and subclavian veins, such as those by Lowenstein[22] and Lahaussois.[23] It seems reasonable to assume that a sudden backward motion of the clavicle, or a sustained backward position of the clavicle, with elevation of the first rib, might produce trauma of the subclavian vein sufficient to cause this mysterious, spontaneous thrombosis. An excellent illustration of this possibility is shown in the case of a normal individual, described in a personal communication from Robb and Steinberg.[24] This man developed a thrombosis of the subclavian and axillary veins after Diodrast[25] had been injected for the purpose of studying the anatomy of his heart and great vessels. The blood containing the Diodrast was held for approximately 9 seconds at the medial portion of the superior edge of the first rib,

and the thrombosis resulted from the irritation caused by the high iodine content of this blood. Fig. 13 (by courtesy of Robb and Steinberg) was taken shortly after the blood had passed the obstruction; the cause of the obstruction had not been previously understood, but, judging from the foregoing discussion, it might have resulted from compression of the subclavian vein, either by the first rib or the clavipectoral fascia as it passes over the first rib. One may note from the figure that the region of compression, where the obstruction occurred, is still apparent.

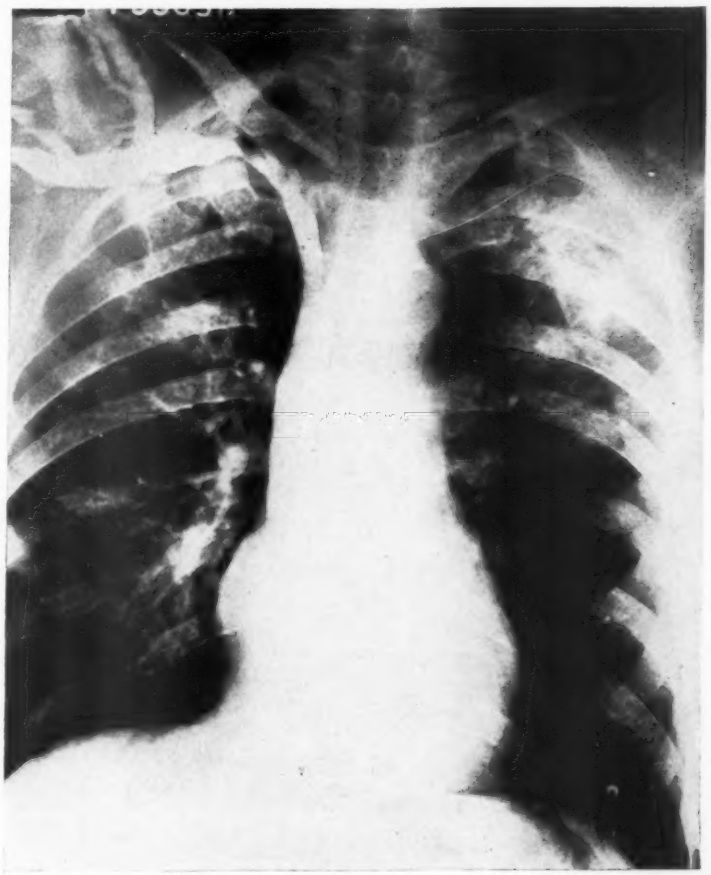


Fig. 13.—Injection of Diodrast in a normal subject, with arm elevated, showing compression of the subclavian vein at the upper margin of the medial portion of the first rib (courtesy of Drs. Robb and Steinberg).

CONCLUSIONS

1. A description of the normal venous pattern of the anterior chest wall is given. It is indicated that the commonest form of the pattern in the upper chest is a series of approximately horizontal veins connecting the cephalic and basilic and possibly the axillary veins to the perforating veins of the first, second, third, and fourth intercostal spaces and the external jugular veins.

2. Prominent veins on the anterior chest wall are seen at all ages and are extremely common after the age of 50 years.

3. It is believed that compression and partial obstruction of the subclavian vein between the clavicle and the first rib anterior to the scalene tubercle are the commonest cause of such prominent venous distention. Compression of the vein by tension on the clavipectoral fascia is an alternate explanation of the obstruction in this region. The veins serve as collaterals which carry part of the blood from the upper arms to the internal mammary and jugular veins when the axillary and subclavian veins are partially obstructed in this way. In one case, Diodrast visualization of blood leaving the median cephalic vein substantiated the explanation suggested.

4. It is generally possible, by study of the venous pattern and the direction of blood flow, to differentiate this partial obstruction of the subclavian vein from obstruction of the innominate vein or the superior vena cava, and likewise from the distention of the veins of the chest which sometimes occurs during and after lactation.

5. The mechanism which produces compression of the subclavian vein consists of a projection of the first ribs laterally and anteriorly, and backward and upward thrust of the clavicles. Patients presenting prominent chest veins, therefore, generally have broad, and often deep, chests and erect postures, with shoulders held backward. A high thoracic kyphosis or a slouched posture generally lowers the clavicles and moves them anteriorly, away from the ribs, preventing encroachment on the subclavicular space. Thoracic scoliosis, by thrusting the ribs upward and laterally, is often accompanied by unusually prominent, but asymmetrical, anterior chest veins, and presumably by subclavian vein obstruction on the same side as the convexity of the spine.

6. Partial obstruction of the subclavian arteries produces a thrill and murmur over the arteries, and, occasionally, unilateral or bilateral lowering of brachial blood pressure. Numbness of the arms occurred in two cases, but whether it was caused by arterial compression, partial involvement of the nerve trunks, or by some irrelevant factor could not be determined.

7. Slight edema of the arm in one patient was the only clinical disturbance apparently caused by the subclavian vein compression in the entire series of cases studied.

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THE RESPONSE OF NORMAL DOGS AND DOGS WITH EXPERIMENTAL HYPERTENSION TO A STANDARD COLD STIMULUS*

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SINCE the cold-pressor test of Hines and Brown[1] has gained wide recognition in the study of human hypertension, it was thought worth while to ascertain what the response of dogs with experimental hypertension might be to such a standard pressor stimulus. In the event that such animals gave positive pressor responses, the underlying physiologic mechanism could be more precisely determined than is feasible in human subjects.

METHOD

Full-grown mongrel dogs of both sexes, weighing from 10 to 16 kilograms, were used. The unanesthetized dogs were trained to lie quietly on the right side while blood pressure measurements were made by the indirect method described by Kolls[2] and perfected by Wood and Cash.[3] Arterial pressure was recorded directly and continuously in a number of other experiments by means of the optical manometer devised by Hamilton, Brewer, and Brotman.[4] The cold stimulus was applied by immersing the clipped left foreleg of the dog halfway up to the elbow in a jar of water kept at a temperature of 3° C. When the indirect method was used, systolic and diastolic pressures were measured just before, during, and immediately after immersion of the foreleg in ice water for two to three minutes. When femoral arterial pressure was recorded directly, continuous systolic and diastolic levels before, during, and after immersion of the forelimb for one or two minutes were obtained. The maximal change attained while the foreleg was in ice water was taken as the index of the response. The pulse rate was recorded graphically with both methods of blood pressure measurement.

Studies were carried out on normal dogs and on dogs with experimental chronic hypertension of two different types. The first, which we shall refer to as "renal hypertension," resulted from constriction of the renal arteries with silver clamps by the method of Goldblatt, et al.[5] The second type was produced by transection of both carotid sinus and both depressor nerves, as described by Hering,[6] Koch and Mies,[7] Heymans,[8] and others; it will be designated as "hypertension from buffer nerve section." The operative procedures employed in producing this form of hypertension were carried out in several stages to avoid sudden cardiac or respiratory failure. The carotid sinus nerves were severed, and the common, internal, and external carotid arteries stripped of their sheaths for a centimeter or two above and below the bifurcation. The arterial walls were then painted with a 5 per cent solution of phenol and washed with alcohol to destroy any nerve fibers which might possibly have remained. The left vago-sympathico-depressor cervical trunk was completely divided, and a 2 cm. piece removed in order to delay nerve regeneration. The medial third of the right vago-sympathico-depressor trunk was cut through, and a similar length removed. By this means the right vagus nerve was left intact,

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and the depressor fibers (and some of the sympathetic fibers) destroyed. It is not always easy to carry out the latter step, but in some dogs the depressor fibers are partially separated from the remainder of the trunk by a natural line of demarcation. In the remaining animals, the function of the fibers transected was demonstrated by the animal's postoperative course; if the dog developed hypertension, most of the right depressor fibers had been destroyed, whereas if the dog developed gastric symptoms without hypertension and died, more vagus than depressor fibers had been severed.

RESULTS

Cold tests were carried out on a total of eighteen animals. The results of 325 tests in which arterial pressure was recorded indirectly are listed in Table I. In six dogs, tests were performed repeatedly, both before and after the production of renal hypertension, and, in two, both before and after hypertension caused by buffer nerve section. Two dogs were tested in the normal state only, seven only *after* renal hypertension had been established for six months to two years, and in one animal tests were carried out from four to fourteen months after the production of hypertension by buffer nerve section. Table II lists the results of thirty-five cold tests performed on eleven of the dogs whose arterial pressure was measured directly.

THE COLD TEST IN DOGS WITH NORMAL ARTERIAL PRESSURE

One hundred thirty-one cold tests were performed on ten normal dogs, measuring pressure by the indirect method, and, from these data, "positive" and "negative" tests were differentiated. We have followed Hines and Brown[1] in defining a positive cold test as one in which a rise exceeding 22 mm. of mercury in either systolic or diastolic pressure, or both, follows the application of the cold stimulus. A negative cold test, on the other hand, is one in which systolic and diastolic pressure rise less than 22 mm. after the cold stimulus has been applied, or one in which a fall in pressure occurs.

One hundred nine, or 83.2 per cent of the tests performed on normal dogs, were negative (Fig. 1*A*). The mean change in arterial pressure in all of the negative tests was +2.5 mm. of mercury, systolic, and + 4.4 mm., diastolic. The remaining twenty-two, or 16.8 per cent, of the cold tests on normal dogs were positive. The mean pressure rise in these positive tests was + 36.9 mm. of mercury, systolic, and + 27.7 mm., diastolic. Within two minutes of withdrawing the paw from the ice water, the blood pressure had returned to the control level in almost every instance.

Most of the positive results were obtained when the dogs were first being accustomed to the test. Tests were carried out repeatedly on each animal, at intervals of a day to a week; the first five consecutive tests performed on each dog constituted the training period, and are referred to as "early tests"; all subsequent ones are called "late tests." Of forty-five early tests, thirteen, or 28.9 per cent, were posi-

TABLE I

325 COLD TESTS IN WHICH BLOOD PRESSURE WAS RECORDED INDIRECTLY

STATE OF ANIMAL		DOG NO.	AVERAGE CONTROL B. P.	TOTAL NO. OF COLD TESTS	POSITIVE COLD TESTS					NEGATIVE COLD TESTS		
					TOTAL NO.	AMONG EARLY TESTS[1]	AMONG LATE TESTS[2]	MEAN CHANGE IN SYSTOLIC B. P. MM. Hg	MEAN CHANGE IN DIASTOLIC B. P. MM. Hg	TOTAL NO.	MEAN CHANGE IN SYSTOLIC B. P. MM. Hg	MEAN CHANGE IN DIASTOLIC B. P. MM. Hg
Normal control		10	208 /116	14	4	4	0	+30	+34	10	+1	+8
		19	182 / 85	11	1	1	0	+36	+16	10	+7	+8
		21	129 / 64	27	6	3	3	+46	+32	21	+5	+6
		22	149 / 77	15	0	0	0	–	–	15	+7	0
		23	155 / 95	2	1	1	0	+30	+38	1	+12	+10
		24	177 / 91	6	0	0	0	–	–	6	+5	+2
		25	165 / 74	6	1	1	0	+31	+19	5	+8	+14
		26	171 / 75	34	6	2	4	+38	+32	28	–3	+3
		27	188 / 96	13	3	3	0	+37	+7	10	–5	+1
		35	184 / 88	3	0	0	0	–	–	3	+3	+6
Renal hypertension	A. Dogs accustomed to cold test before hypertension was produced	10	264+/171*	4	1	–	1	+12	+38	3	?*	+9
		19	234 /126	22	0	–	0	–	–	19	+8	+9
		21	210 /120	11	1	–	1	+24	+13	10	+4	+7
		22	177 / 99	2	0	–	0	–	–	2	+11	+3
		26	242 /135	2	0	–	0	–	–	2	–33	+4
		35	213 /135	4	0	0	0	–	–	4	+9	+6
	B. Dogs in which hypertension was established before cold tests were begun	3	262+/149*	18	4	3	1	+34*	+16	14	0*	–12
		5	249 /127	15	6	4	2	?*	+34	9	+1	+4
		9	221 /119	26	12	4	8	+32*	+28	14	+9	+1
		28	254 /162	7	1	1	0	+37	+16	6	+10*	–3
		29	257 /142	6	3	3	0	?*	+61	3	+8*	+13
		30	275+/117*	10	0	0	0	–	–	10	?*	0
		31	256 /154	10	2	2	0	?*	+35	8	+1	–9
Hypertension caused by buffer nerve section	A. As A above	25	206 /125[3] 185 / 98[4]	21	10	–	10	+39	+39	11	0	+1
		27	243+/163*	11	3	–	3	+33	+11	8	–13	–11
	B. As B above	15	194 /125	25	14	4	10	+40	+41	11	+6	+6

[1]"Early tests" = the first five cold tests to which the dog was subjected.
[2]"Late tests" = all subsequent cold tests after the first five.
[3]Average B. P. during the period of the 10 cold tests (6 positive, 4 negative) immediately following buffer nerve section.
[4]Average B. P. during the period of the succeeding 11 cold tests (4 positive, 7 negative).
*Systolic pressure was at times above the top of the manometer (270 to 280 mm. Hg); such instances have been omitted from the averages.

tive, whereas, of eighty-six late tests, only nine, or 10.4 per cent, were positive. Thus, after normal dogs had become fully accustomed to the procedure, there was no pressor response exceeding 22 mm. of mercury in 89.6 per cent of the tests. In a considerable number of the negative tests, arterial pressure actually fell in response to the cold stimulus. The data for each dog, together with the mean pressure changes in positive and negative tests, are given in Table I.

Three of the ten normal dogs never reacted positively in any of a total of twenty-four tests. One animal (dog 10) was of particular interest because it had a spontaneously high pressure, which had remained at an average level of 208/116 mm. Hg for a year before cold tests were begun. This is the highest arterial pressure that we have encountered in a "normal" dog, i.e., one which had not been operated on. Seventy-one and four-tenths per cent of this dog's fourteen cold tests were negative, so that it conformed quite closely to the average of the group, and exhibited no significant difference which could be attributed to the fact that its hypertension was spontaneous. In no instance did an individual dog show a preponderance of positive cold tests, and so correspond to the "normal hyperreactors" of Hines and Brown. The nine cold tests performed on normal dogs in which the blood pressure was measured by the direct method were all negative (Table II and Fig. 1 *A*).

TABLE II

35 COLD TESTS IN WHICH BLOOD PRESSURE WAS RECORDED DIRECTLY

STATE OF ANIMAL		DOG NO.	AVERAGE CONTROL B. P.	TOTAL NO. OF COLD TESTS	POSITIVE COLD TESTS	NEGATIVE COLD TESTS		
					TOTAL NUMBER	TOTAL NUMBER	MEAN CHANGE IN SYSTOLIC B. P. MM. Hg	MEAN CHANGE IN DIASTOLIC B. P. MM. Hg
Normal control		21	146/85	3	0	3	+1	+8
		26	184/100	5	0	5	−8	−2
		36	185/106	1	0	1	−15	−6
Renal hypertension	A. Dogs accustomed to cold test before hypertension was produced	21	222/138	4	0	4	+5	+4
		26	232/163	2	0	2	+3	+3
		36	234/151	1	0	1	−3	−5
	B. Dogs in which hypertension was established before cold tests were begun	3	300/175	3	0	3	−20	−3
		5	218/143	1	0	1	+3	+7
		9	246/141	1	0	1	+11	+9
		19	244/148	3	0	3	+1	−1
		30	265/187	1	0	1	+22	−17
		35	206/130	2	0	2	+8	+15
Hypertension caused by Buffer Nerve Section		15	271+/189	3	0	3	+2	+10
		27	298+/201	5	0	5	−7	−15

THE COLD TEST IN DOGS WITH RENAL HYPERTENSION

One hundred thirty-seven cold tests in which pressures were measured indirectly were carried out on thirteen dogs during the period of well-marked hypertension following renal artery constriction. Six of these animals had already been trained by repeated cold tests during the control period, when their arterial pressure was normal (see Table

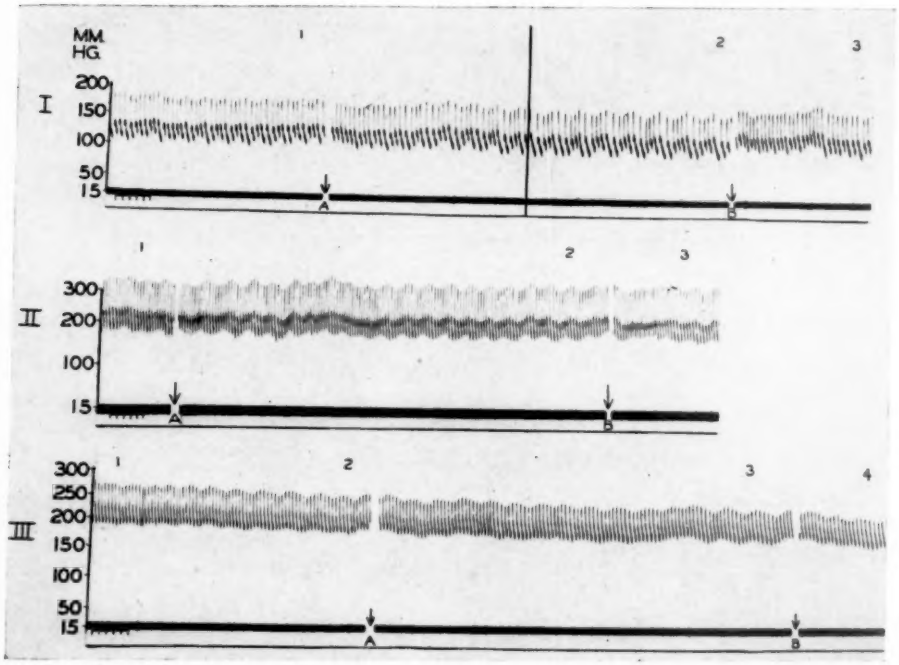

Fig. 1.—The cold test in dogs with normal and experimentally elevated blood pressure, as recorded by the Hamilton Optical Manometer.

At *A* in each record the dog's left foreleg was immersed halfway up to the elbow in water at a temperature of 3° C.; at *B* the foreleg was withdrawn from the ice water.

The mm. of mercury scales are based on calibrations of the manometer made immediately after each record was taken. Note that equal increments of pressure at different levels do not deform the copper-beryllium membrane by equal amounts. The baseline at 15 mm. corrects for the difference in level between the dog's heart and the baseline mirror. The time lines on the original records at ⅕ second intervals are difficult to see when reduced; a scale of five one-second intervals has been constructed on each record.

I. Dog 36, female, weight 12.4 kg.; Jan. 21, 1939; normal control.
   1. End of control period. B.P. 185/106. Pulse rate 87.
   2. End of two-minute immersion of foreleg in ice water. (A one-minute-long section of the record which showed no change has been cut out at the black line between *A* and *B*.) B.P. 170/100. Pulse rate 74.
   3. Fifteen seconds after foreleg was removed from ice water. B.P. 179/106. Pulse rate 78.

II. Dog 3, male, weight 11.5 kg.; Jan. 25, 1939; renal hypertension.
   1. End of control period. B.P. 325/175. Pulse rate 135.
   2. End of one-minute immersion of foreleg in ice water. B.P. 322/175. Pulse rate 132.
   3. Ten seconds after foreleg was removed from ice water. B.P. 322/177. Pulse rate 128.

III. Dog 27, female, weight 12.5 kg.; Jan. 21, 1939; hypertension caused by buffer nerve section.
   1. Beginning of control period. B.P. 271/184. Pulse rate 126.
   2. End of control period. B.P. 253/177. Pulse rate 121.
   3. End of one-minute immersion of foreleg in ice water. B.P. 232/167. Pulse rate 104.
   4. Ten seconds after foreleg was removed from ice water. B.P. 218/157. Pulse rate 100.

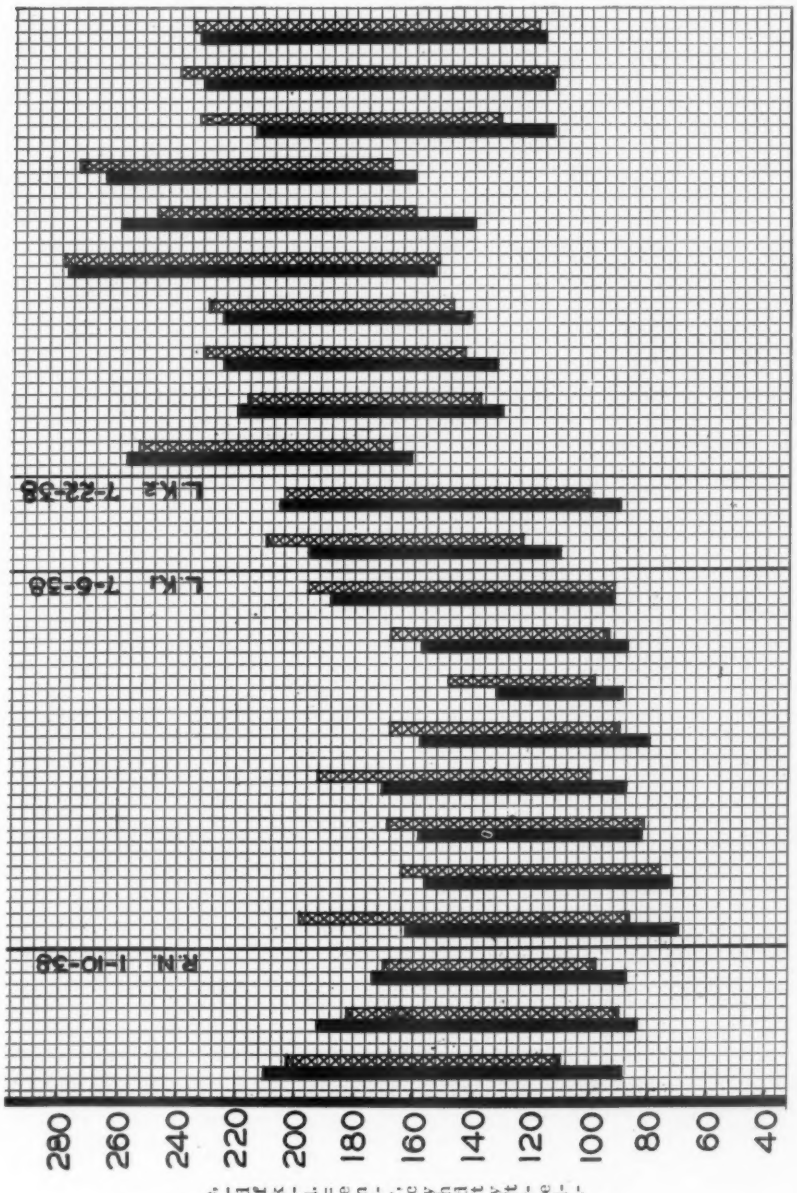

Fig. 2.—Dog 19, female, weight 11.3 kg. Successive cold tests before and after the production of renal hypertension. Black columns = arterial pressure during control period. Cross-hatched columns = arterial pressure while foreleg was immersed in ice water. Arterial pressure measured indirectly, systolic and diastolic pressures represented by top and bottom of each column. *RN* = Right-sided nephrectomy. LK_1 = Left main renal artery lightly constricted. LK_2 = Left main renal artery moderately constricted. The fourth cold test was positive, all the others negative.

I, Group A, and Figs. 2 and 3). After hypertension was produced in this group, forty-three out of forty-five cold tests were negative. Group B consists of seven dogs which were never subjected to the cold test until after hypertension became well established. Among these animals hyperreaction was more common than in normal dogs during the training period. Of twenty-eight positive responses obtained among a total of ninety-two cold tests, seventeen occurred during the thirty-five early tests. The early tests therefore gave an equal number of

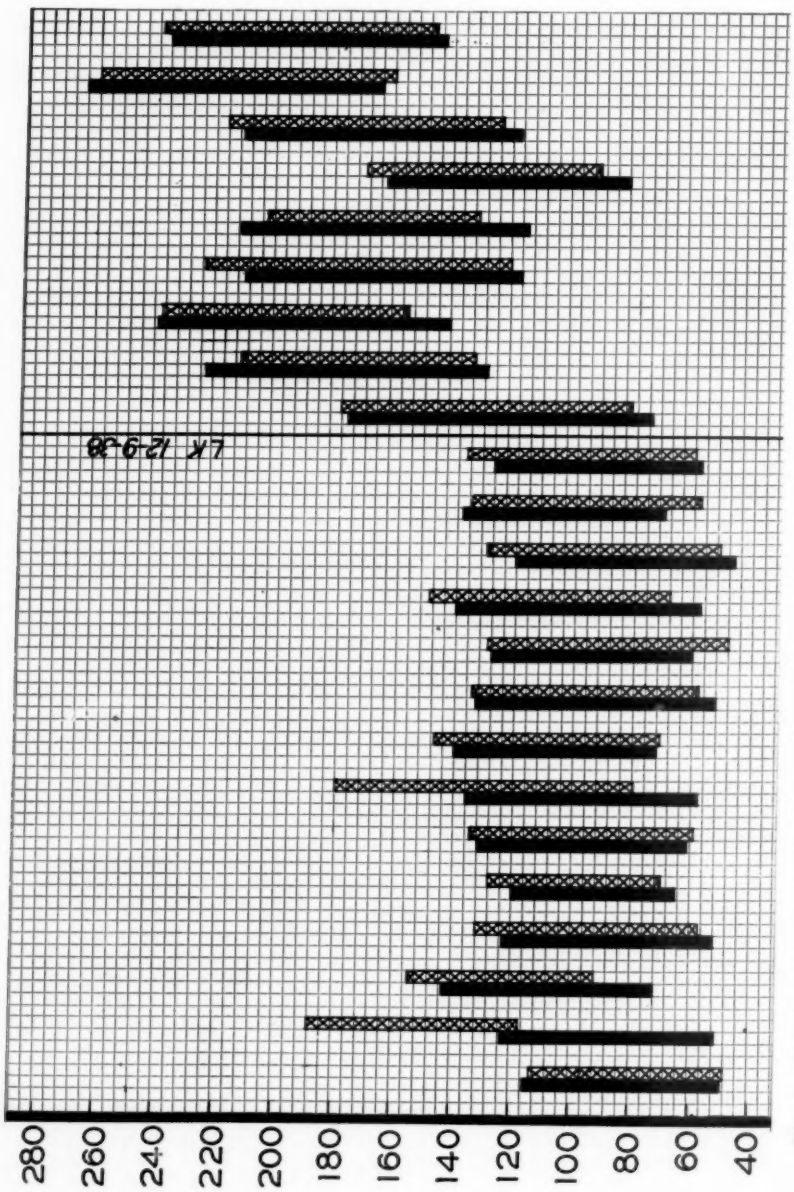

Fig. 3.—Dog 21, female, weight 12.4 kg. Successive cold tests before and after the production of renal hypertension. Black columns, cross-hatched columns, as in Fig. 2. Right nephrectomy performed previously. *LK* = Left main renal artery constricted. For the sake of conciseness, the first thirteen (control) and the last two cold tests (during renal hypertension) have been omitted. Only two of the cold tests charted are positive.

positive and negative reactions. Among the fifty-seven late tests, however, there were only eleven positive responses.* Combining the late tests in Groups A and B, 100 cold tests, in all, were performed on dogs with renal hypertension after they had become accustomed to the procedure; 87 per cent of the tests were negative, and 13 per cent were positive. This is entirely comparable with the response which occurs in normal trained dogs. Thus, there is no increased reactivity to cold in dogs with renal hypertension as compared with normal dogs when both groups of animals have been trained to undergo the test, and elevation of arterial pressure by constriction of the renal arteries did not transform normal, negatively reacting dogs into hyperreactors.

Of eighteen cold tests on nine dogs with renal hypertension in which arterial pressures were measured directly, all were negative (Table II and Fig. 1 *B*). All of the animals had been thoroughly accustomed to ice water when this group of cold tests was undertaken, so that no "early tests" were included.

THE COLD TEST IN DOGS WITH HYPERTENSION CAUSED BY BUFFER NERVE SECTION

Transection of both carotid sinus nerves and both aortic depressor nerves in dogs results in another form of chronic experimental hypertension which has been little studied in this country. Despite numerous reports from abroad on this subject, the dynamics of the circulation under such conditions have not been adequately described. We have had under observation for twenty-three months, fifteen months, and ten months, respectively, three dogs with all four buffer nerves cut. Briefly, we have found that the four nerve transections transform a normal dog into an animal in which the arterial pressure frequently exceeds 300/200 mm. of mercury, with a pulse rate of about 200 per minute despite the absence of all external signs of excitement. In most instances, during the course of five minutes' observation and thereafter, the arterial pressure and pulse rate gradually decline from these very high levels, but still remain well above normal.† In contrast, the arterial pressure and pulse rate of normal dogs and dogs with renal hypertension remain very constant during the first five minutes of observation. In dogs whose buffer nerves have been cut, spontaneous fluctuation of pressure and pulse rate is more common, especially when the indirect method of measuring arterial pressure is used. Measurements made by the indirect method show that the blood pressure in these animals falls after a time to levels lower than have

*Dog 9 reacted positively to four out of the five early tests and to twelve out of twenty-one late tests. The serial numbers of the positive tests were 1, 2, 3, 4, 7, 8, 10, 12, 14, 16, 18, 25. The decreasing frequency of the positive tests toward the end of the series, plus the fact that in tests 1, 2, 3, 4, 7, and 10 both systolic and diastolic levels rose more than 22 mm. while in the remaining tests only the systolic pressure did so, indicates that this animal's response resembles the others save that the training period was more prolonged.

†It has been reported by Samaan[9] that in such dogs the arterial pressure approaches normal levels during deep sleep.

been recorded with the direct method. A few minutes later it may become high again. Thus, it is apparent that the arterial pressure in dogs with hypertension caused by buffer nerve section is less stable than it is in normal dogs and in dogs with renal hypertension.

Of fifty-seven cold tests performed on three dogs, using the indirect method of measuring arterial pressure, twenty-seven were positive and thirty were negative. There were thirteen positive tests on two dogs which had been thoroughly accustomed to cold tests before the operation and had had no positive late tests during the control period (Figs. 4 and 5). In the third dog, ten out of twenty late cold tests were positive. However, in none of eight tests in which the blood pressure was recorded continuously by the Hamilton method was there a rise in systolic or diastolic pressure of more than 22 mm. (Table II and Fig. 1 *C*), save once, when a momentary rise occurred just before and during the placing of the paw in ice water, and this disappeared a few seconds later. This rise was apparently caused by the excitement and activity produced by placing the paw in ice water, rather than by the cold stimulus itself, and therefore is not considered a positive test.

THE EFFECT OF THE COLD TEST ON THE CARDIAC RATE

Without presenting the data in detail, it may be stated briefly that, whenever there was no blood pressure response to cold, the cardiac rate remained essentially the same, or became slower. When, on the other hand, there was a pressor response, the cardiac rate became accelerated, and returned to normal with the blood pressure. This relationship seemed to hold true regardless of whether the dog was normal or had either form of experimental hypertension.

DISCUSSION

Judging from our studies, it is clear that when a normal dog is subjected to the same stimulus that is used in the cold-pressor test in man, the pressor response is of no more than minimal intensity in 83.2 per cent of the tests. In 78.1 per cent of the tests on dogs with renal hypertension the results were negative. In dogs with hypertension produced by buffer nerve section, 52.7 per cent of all cold tests were negative when the blood pressure was measured by the indirect method, whereas all of eight tests were negative when the pressure was measured by the direct method. Among normal dogs and dogs with renal hypertension, positive tests occurred most frequently during the training period, whereas, in the dogs thoroughly accustomed to ice water, positive responses were rare. There were no normal dogs which gave persistently positive responses, as human "hyperreactors" do. Why the cold tests were positive in 47.3 per cent of the dogs whose buffer nerves had been transected is not clear; in contradistinction to the results in the other two groups of animals, such positive tests fre-

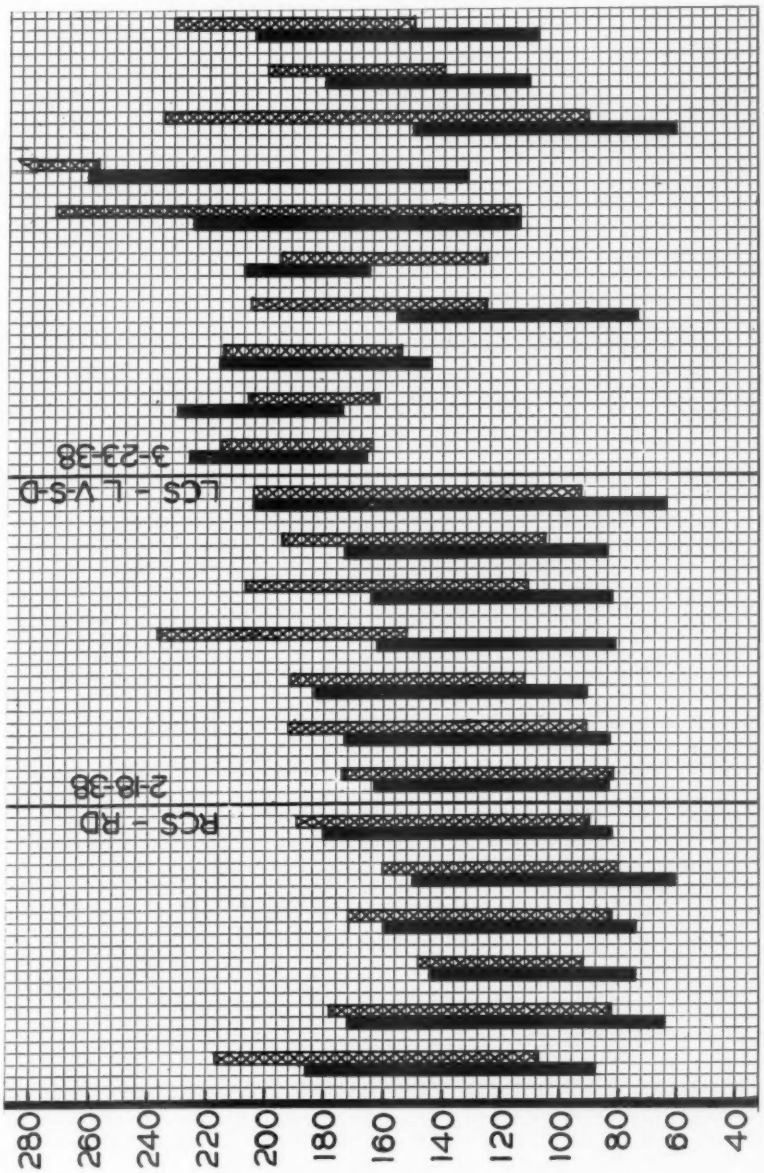

Fig. 4.—Dog 25, female, weight 11.8 kg. Successive cold tests before and after the production of hypertension by section of the four buffer nerves. Black columns, cross-hatched columns, as in Fig. 2. *RCS* = Right carotid sinus nerve transected. *RD* = Right depressor nerve transected. *LCS* = Left carotid sinus nerve transected. *L V-S-D* = Left vago-sympathico-depressor nerve trunk transected. Cold tests 1, 10, 11, 13, 17, 19, 20, 21, 22, and 23 were positive. No cold tests were made with the direct method of measuring pressure during this period. Later, the dog's B.P. fell somewhat, and most of the cold tests became negative. In Figs. 4 and 5, cold tests were not performed until the dog had been quiet on the table for ten or more minutes, so that the control pressures for the cold tests were usually considerably lower than the initial pressures.

quently appeared even when the dogs were well trained. The instability of the pressure and the fact that there were no positive cold tests among those in which the arterial pressure was recorded directly leave the situation obscure. However, it is evident that neither type of experimental hypertension yielded the almost uniformly positive pressor responses reported by Hines and Brown[1] in cases of essential hypertension in man.

Were the cold tests in these experiments strictly comparable to those which have been performed on human subjects? The bare, sensitive, human palm and forearm are strikingly different from the thick toe pads and hair-covered foreleg of the dog. Since the dog is adapted to run through snow and over ice, it is likely that the cold receptors in the dog's leg are neither as numerous nor as sensitive as those of the human arm. Untrained dogs gave evidence of some temperature discrimination by withdrawing their forelegs more frequently from ice water than from water at room temperature. It is, however, possible that the intensity of the stimulus in the dog is so much less than in man that no corresponding pressor response is produced.

If this is true, how may we account for the not infrequent positive responses in the early tests? Although the dogs appeared quiet, the positive responses may have represented the effect of mental agitation, apprehension, or discomfort, rather than a specific pressor reaction to the cold stimulus. In this regard, certain investigators[10, 11] of the cold test in human subjects believe that the pressor response is merely a reflection of the discomfort or pain undergone by the individual, and also bears a relationship to the patient's age, but Hines and Brown believe that a positive cold test represents an exaggeration of normal vasomotor reactions, so that any type of stimulation results in an excessive response of the blood pressure which is an abnormality characteristic of that individual.

Whatever the explanation, the first test performed on a dog was certainly more often positive than any of the subsequent ones, so that training is a factor in determining whether a given test will be positive or negative. The untrained dogs with renal hypertension reacted positively half of the time. Is it fairer to compare this group, or the negatively reacting trained group of dogs with renal hypertension, with patients with essential hypertension? The answer depends upon whether the positive response to cold in a human subject with essential hypertension is a constant one, or whether more and more negative responses are obtained as the test is repeated at intervals of a few days, as in dogs. Hines and Brown[1] report that in twenty subjects with essential hypertension the cold test was repeated one or more times, with consistently positive responses, after intervals of from three months to three years, but here the training was neither intensive nor prolonged. One patient with normal pressure who reacted posi-

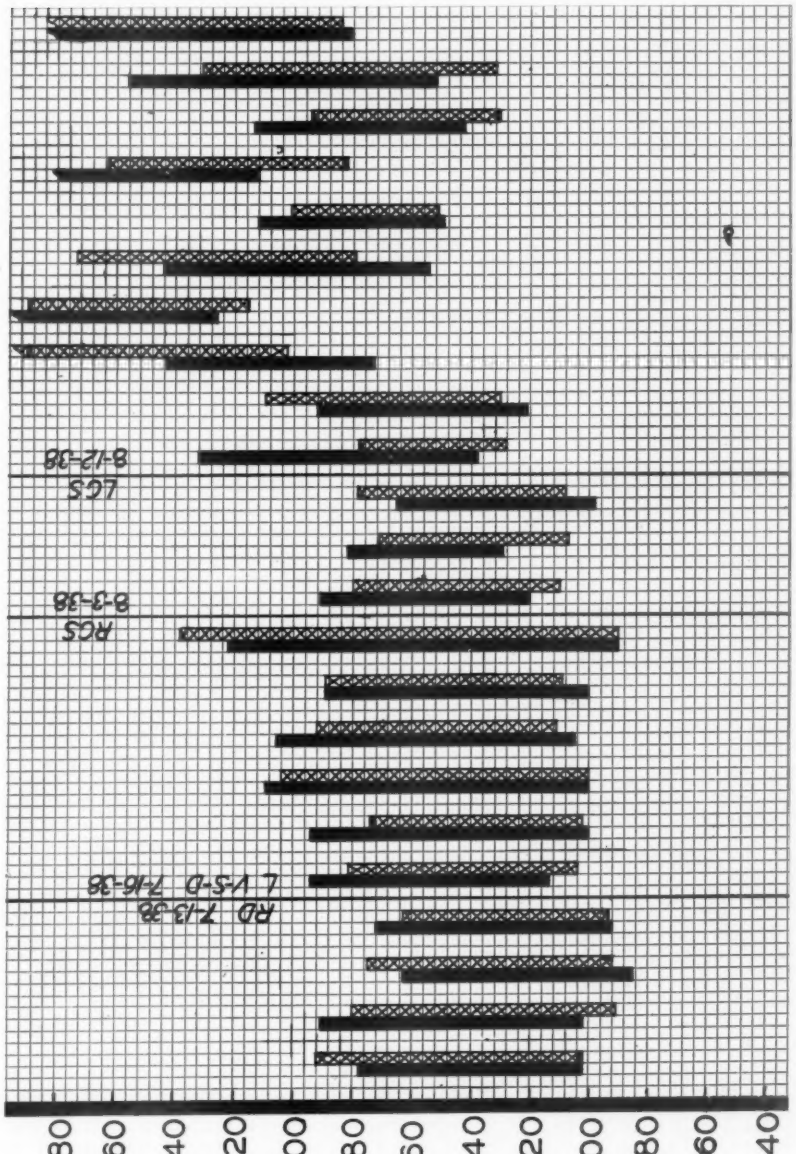

Fig. 5.—Dog 27, female, weight 11.7 kg. Successive cold tests before and after the production of hypertension by section of the four buffer nerves. Black columns, cross-hatched columns, as in Fig. 2. *RD* = Right depressor nerve transected. *LV-S-D* = Left vago-sympathico-depressor nerve trunk transected. *RCS* = Right carotid sinus nerve transected. *LCS* = Left carotid sinus nerve transected. The first nine (control) cold tests have been omitted for the sake of conciseness. Two of the cold tests following buffer nerve section were positive.

tively was subjected to the cold test fifty-six times in two years and never gave a negative response. No report that a patient with essential hypertension has been so intensively studied has come to our attention, but each of five such patients who were examined in the Johns Hopkins Hospital[12] has had from five to ten cold tests, from two to ten days apart, which were uniformly positive.

The negative response to cold of dogs with renal hypertension may be of considerable significance. Alam and Smirk[13] found that, in contrast to the positive response to cold noted in patients with essential hypertension, patients with renal hypertension (patients with marked impairment in their ability to concentrate urea, and showing strong clinical evidence that the renal lesion was not secondary to the hypertension) gave negative reactions. In contrast to patients with essential hypertension, Hines and Brown[1] state that patients with glomerulonephritis are much less likely to react. Our studies may well indicate that experimental renal hypertension is more closely related to the human forms of hypertension in which renal disease is a known factor, than to "essential" hypertension with apparently normal renal function.

CONCLUSIONS

1. In normal dogs, a standard cold stimulus was followed by a negative pressor response in 83.2 per cent of all of the tests. As the animals became accustomed to the cold test, positive responses grew less frequent, until 89.6 per cent of the late tests were negative.

2. In untrained dogs with renal hypertension, half of the cold tests were positive, but, in trained animals, 87 per cent of the tests were negative.

3. Dogs with hypertension caused by buffer nerve section showed a variable reaction to the cold test, but gave a negative response more often than a positive one.

4. Among the experimental animals, no group was found to correspond with human "normal hyperreactors," nor with human subjects with essential hypertension.

5. A possible relationship between the hypertension in dogs with renal artery constriction and in patients with hypertension secondary to renal disease is discussed.

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MEDIAL DEGENERATION, CYSTIC VARIETY, IN UNRUPTURED AORTAS

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MEDIAL degeneration of the cystic variety has been encountered chiefly in cases of dissecting aneurysm of the aorta; only two cases of this disease in unruptured aortas have been reported.[1, 2] A systematic study of the aorta in a series of 210 routine autopsies disclosed cyst formation in the media in seven instances. Brief reference to them was made in a recent communication.[3] It is now proposed to enlarge on these cases and, more particularly, to discuss the pathogenesis of the lesion.

MATERIAL AND METHOD OF STUDY

In each instance, the ascending aorta and arch were cut completely into 6 or 7 transverse, serial blocks, each of which included the entire circumference of the vessel. Two to four long, longitudinal strips were also cut from the descending thoracic and abdominal aorta. From each block two sections were prepared, of which one was stained with hematoxylin and eosin, and the other with Weigert's elastic tissue stain. Some sections were subsequently decolorized and restained by the Masson trichrome technique.

In Table I, only pertinent clinical and gross pathologic changes are recorded. None of the patients had clinical or pathologic evidence of syphilis. All were beyond 44 years of age. The first patient had been under medical observation for twelve years; hypertension was not present until the last two. The second patient was in the hospital for two days and died from intestinal obstruction caused by twisting of the ileum about a fibrous adhesion. In the third case the illness began with sudden precordial pain and shock. Death followed in five days. The fourth patient entered the hospital in shock and died two hours later. The fifth patient had an acute illness lasting seventeen days. It began with an acute otitis media which was later complicated by multiple joint involvement and cerebral meningitis. The sixth patient suddenly collapsed two hours before admission, and in a few hours was dead. The seventh patient had been under observation one day, when he died. His sole complaint consisted of shortness of breath.

Other clinical data in these cases were either irrelevant or unobtainable.

MICROSCOPIC OBSERVATIONS

The type, relative number, location, and distribution of the medial lesions are indicated in Fig. 1. It will be noted that they were confined to the ascending aorta and arch. In Case 1, the lesions were found exclusively in the lower ascending portion of the aorta. They appeared to best advantage in preparations stained for elastic tissue. In these, numerous, irregular, frequently zizgag, areas were seen (Fig. 2 *A*) throughout the width of the media. They were characterized chiefly

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TABLE I

CASE	SEX	AGE	B.P.	CAUSE OF DEATH	HEART SIZE	CORONARIES	AORTA	KIDNEY
1	M	48	206/110	Cerebral Hemorrhage Ruptured miliary aneurysm	E.H.* 560 Gm.	Thin	Smooth elastic	Grossly normal
2	M	44	No record	Intestinal obstruction	315 Gm.	Severe atherosclerosis	Smooth	Normal
3	F	70	130/ 80	Coronary occlusion	E.H. 500 Gm.	Coronary thrombosis Myocardial infarct	A few scattered atheromatous patches	Finely granular Arteriolonephrosclerosis
4	M	75	No record	Coronary occlusion	E.H. 435 Gm.	Old and recent thrombosis	Severe intimal sclerosis	Small, granular Arteriolosclerosis
5	M	50	142/ 80	Cerebral meningitis Acute vegetative endocarditis	E.H. 470 Gm.	Thin	Smooth elastic	Normal
6	M	67	230/140	Cerebral hemorrhage	E.H. 500 Gm.	Severe atherosclerosis	A few scattered atheromatous patches	Small, granular with necrotizing arteriolosclerosis
7	M	61	170/ 72	Acute bacterial endocarditis	No E.H.	Thin	Smooth	Normal size Smooth Arteriolosclerosis

*Enlarged Heart.

by loss of elastic tissue. Fragments of lamellae persisted in some areas, as did also faintly staining collagen fibers. Muscle cells were at times completely absent, depleted, or normal in number. In places they were clumped and so arranged that their long axis lay perpendicular or oblique to those in normal adjacent areas (Fig. 2 *B*). At times, the only clue to the presence of a lesion from examination of sections stained with hematoxylin and eosin was a slight change in the normal axis of the muscle cell. A basophilic material occupied those areas in which the various elements were partially or completely disintegrated. There was complete absence of cellular reaction, fibrosis, and vascularization in the lesions in this and subsequent cases. In Case 2, five irregular cystic lesions were found in the middle third of the media. Four were about ¼ mm. long and were narrow and parallel to the circumference of the vessel; one was broad, extending obliquely across the media. There was partial to complete absence of elastic tissue in all lesions. In some, occasional well-preserved muscle cells were still present, intermingled with a mucoid material (Fig. 2 *C*). Two closely adjacent degenerated areas, filled with a homogeneous basophilic and eosinophilic material, were found close to the intima in the aorta in Case 3 (Fig. 2 *D*). The aortas in Cases 4, 5, 6, and 7, in addition to mucoid cysts, contained from a few to many areas characterized solely by complete loss of muscle cells and crowding of elastic lamellae. While in most instances there was no further change in these

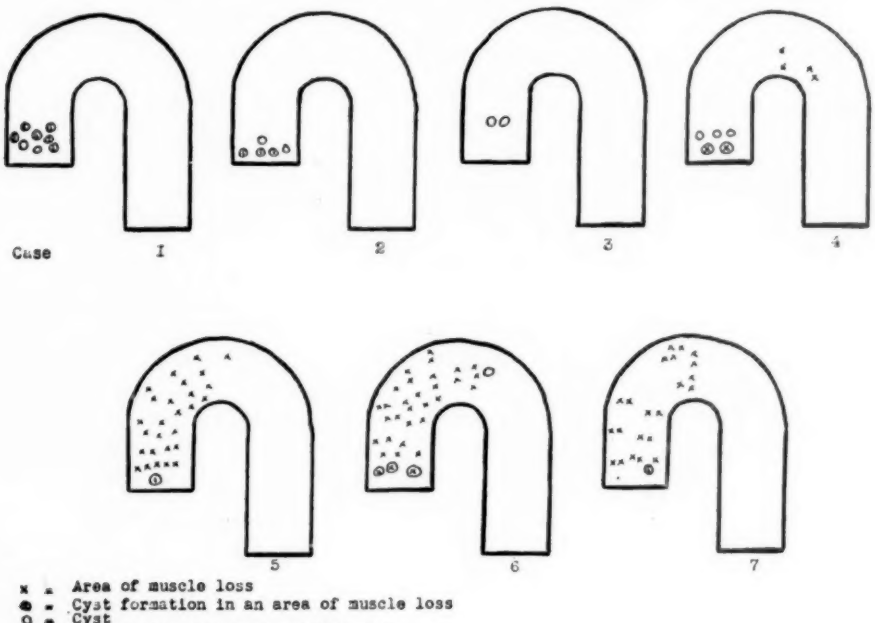
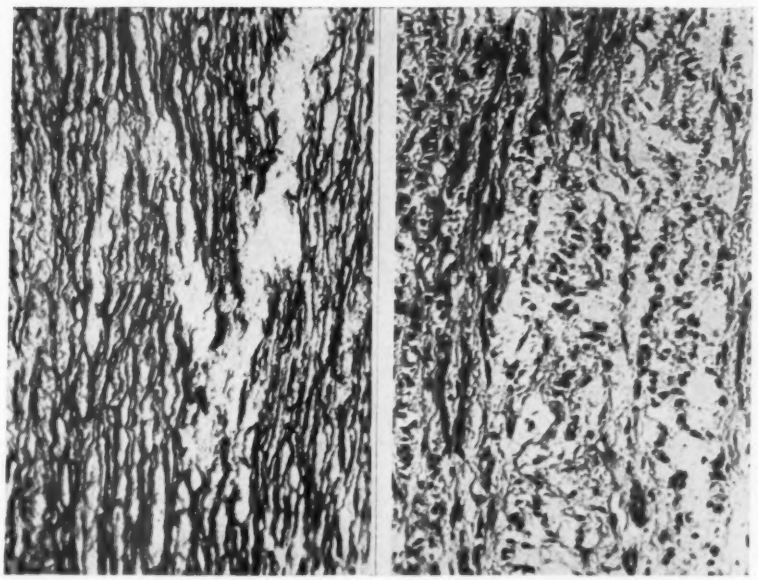
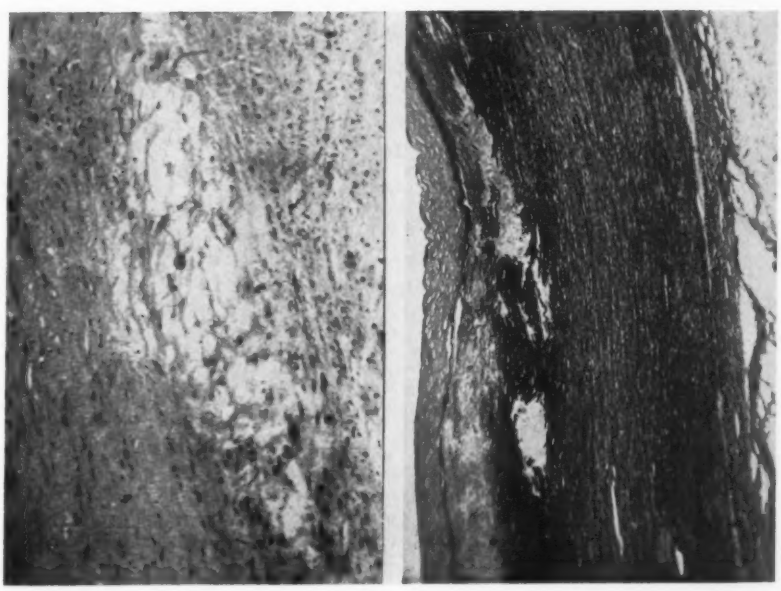


Fig. 1.—Composite drawing or diagram of aortas showing distribution of lesions.



A. *B.*



C. *D.*

Fig. 2.—*A*, Low power; elastic tissue stain (Case 1). Note the zigzag lesion extending across the width of the media. The defect is occupied largely by mucoid fluid. Also present are fragments of elastic tissue and an occasional muscle cell (seen in hematoxylin and eosin stained sections). *B*, Low power; hematoxylin and eosin stain (Case 1). Note irregularity in muscle cell arrangement caused by clumping and change of their axes. A considerable amount of basophilic fluid is present. In the Weigert elastic tissue stained section elastic tissue was found absent from the area. *C*, Low power; hematoxylin and eosin stain (Case 2). Medial lesion located in the middle third at the root of the aorta. Elastic tissue is absent within the lesion. The area is occupied chiefly by a basophilic substance. A few muscle cells and fragments of collagen remain. *D*, Low power; elastic tissue stain (Case 3). Only two cystic areas were found in this case, located near the intima. The contents consist of a mixture of substances—one eosinophilic, the other basophilic.

areas, in Cases 4 and 6, long, narrow, mucoid-filled spaces were found within them (Fig. 3 *A*). However, in both of these cases as well as in the remaining two (5 and 7), there were other cysts which had no relationship to the foci of muscle loss (Fig. 3 *B, C, D*). The intima of the aorta was relatively thin in all but Case 4. Though medial lesions in this case were found beneath intimal plaques, they also occurred independently.

DISCUSSION

The cystic lesions described in this report corresponded in appearance to those encountered in the media of aortas which are the seat of dissecting aneurysm. There was the same absence of cellular reaction and relationship to intimal change and disease of the vasa vasorum.

The term "cystic" is hardly a happy one, for the degenerated areas are not encapsulated. They are bound by media which usually, by virtue of its preservation, gives the lesion a sharply circumscribed appearance. The rarity of this lesion in unruptured aortas is indicated by the fact that it was found in only seven of 210 carefully studied vessels. Neither Cellina[4] nor Weise[5] found it in his studies.

The lesion could easily have been missed had fewer blocks been cut. It was found chiefly at the root of the aorta, just above and beyond the level of the commissures. In one case it was present at the arch. These are the sites of election for spontaneous rupture. Cystic degeneration occurred chiefly in the middle third of the media. However, it was also observed in the inner and outer thirds, as well.

In his paper on medionecrosis, Gsell[6] describes focal areas of muscle necrosis in which, occasionally, he was able to trace further disintegration of elastic tissue and collagen, resulting in the formation of fluid-filled medial defects. Similar observations were made by myself in a series of selected cases of dissecting aneurysm.[7] However, it was obvious at the time that this mechanism alone could not be invoked to explain all cystic lesions, for in many of them muscle cells were still preserved, while the elastic tissue was obviously in a state of disintegration. Similar observations had previously been made by Erdheim[8] and Cellina.[9] The former,[10] recognizing this, attempted to explain cystic degeneration by taking into account the fact that mucoid is normally present in the interlamellar space. He believed that unusual accumulations of this substance caused, first, thinning, and later, dissolution of the bordering lamellae, thus permitting mucoid from adjacent areas to become confluent and form larger pools. Levinson[11] and Moritz[12] were in agreement with this theory. Cellina,[9] however, did not feel that this mechanism explained the cystic degeneration he observed in his own material. He believed, instead, that there occurred a primary injury to elastic lamellae, as a result of which they thinned, disintegrated, and finally disappeared; the prod-

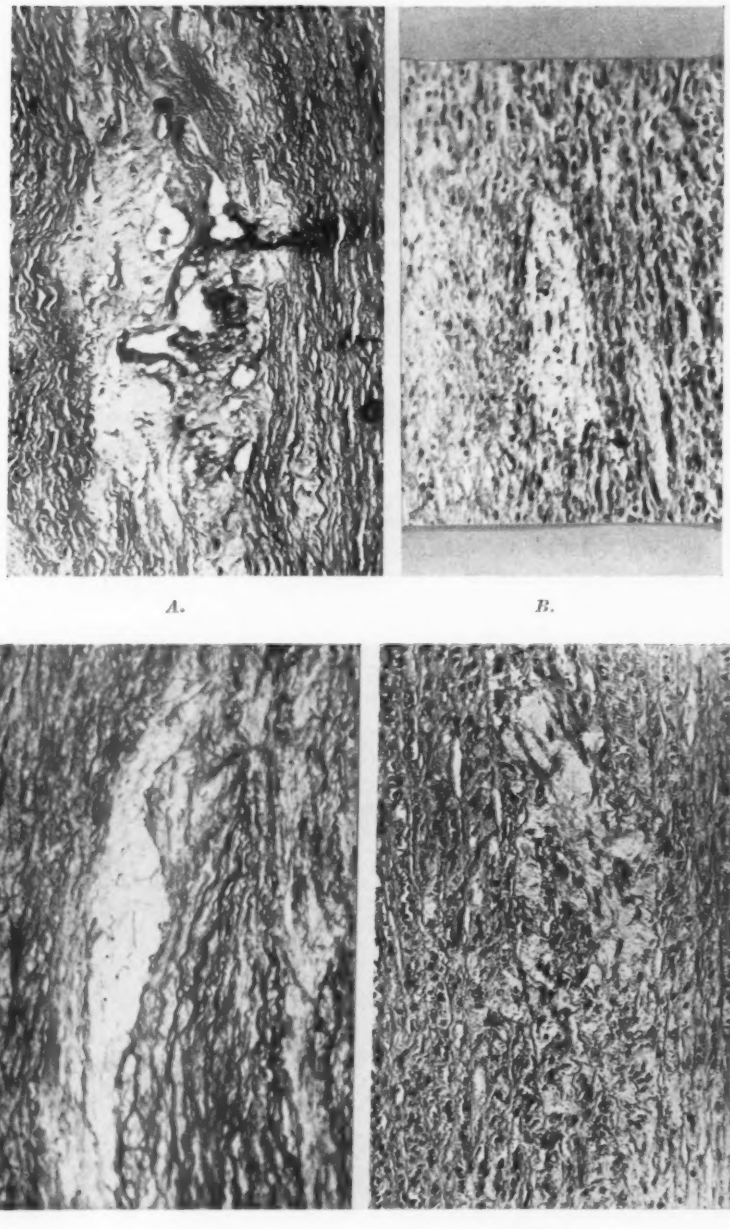


Fig. 3.—*A*, Low power; hematoxylin and eosin stain (Case 4). A mucoid pool found in an area of muscle loss. The media immediately around the pool consists of crowded elastic laminae, between which muscle cells are absent. *B*, Low power; hematoxylin and eosin stain (Case 5). A small, circumscribed, cystic lesion in the middle third of the media, composed of mucoid, fragments of collagen, and a few muscle cells. Elastic tissue is absent. The surrounding media is normal. *C*, Low power; Weigert's elastic tissue stain (Case 6). A medial defect filled with a basophilic material and fragments of elastic tissue. *D*, Low power; hematoxylin and eosin stain (Case 7). A medial defect in which the elastic elements are absent. Muscle cells persist in depleted numbers. Note change in the muscle axes.

ucts of disintegration then gave rise to the basophilic material which formed the contents of the cysts. The elastic tissue disintegration occurred independently of muscle cell change, for in many areas the cells were well preserved.

A study of the seven cases in this report disclosed two instances (Cases 4 and 6) in which fluid-filled clefts were present in areas of muscle loss. In no case could the development of cysts be traced to the mechanism described by Erdheim.[10] In four the cysts bore a resemblance to those described by Cellina.[9]

The occurrence of elastic tissue defects makes it easy to understand the bizarre configuration of some of the lesions observed in this series. From their appearance, one gained the impression that they had been produced by pulling apart of the wall (Fig. 2 *A*). In a vessel like the aorta, which is subject to constant stretching and recoil, and to abrupt and sharp rises in blood pressure, such occurrences would seem inevitable. Thus, in addition to the primary lesions of elastic tissue disintegration, the resulting weakness would lead to others caused by tears. These, if large and numerous enough, or strategically located, would in time cause a major rupture of the vessel wall.

A word must be added concerning the lesions, characterized by the presence of disintegrating elastic tissue, preserved muscle cells, and mucoid, which were encountered in the series of dissecting aneurysms previously reported.[7] At the time, little was said about them, and they were included in the category of regenerated areas, in the sense of Erdheim.[10] This interpretation may possibly hold for areas in which muscle cells are unusually numerous and closely adjacent to each other. However, when one sees, in the same, or other, cases, disintegrating elastic lamellae and practically intact muscle cells side by side, it is more than likely that one is dealing, not with regeneration, but rather with early degeneration. Although it is difficult to understand how an inert substance like elastic tissue can be injured and proceed to disintegrate while the muscle cells remain initially unaffected, it would be still more difficult to interpret the histologic findings in any other way. With this in mind, restudy of the twelve ruptured aortas disclosed this lesion in eleven. The other observations and interpretations remained the same.

SUMMARY AND CONCLUSIONS

1. Seven instances of cystic medial degeneration, found in a systematic study of two hundred ten aortas, are presented.

2. In four of these there were also from a few to many areas of muscle loss. Cystic degeneration in the latter areas was observed in two aortas. In all four, other cystic lesions were independent of foci of muscle loss.

3. In four vessels the earliest change appeared to be disintegration of elastic lamellae.

4. The same was observed in eleven of twelve cases of dissecting aneurysm of the aorta.

5. The composite picture of medial degeneration in any aorta appears to consist of a primary lesion, plus secondary tears resulting from focal weakness which it causes.

6. These, when significant enough, lay the groundwork for major rupture of the vessel wall.

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THE SAPHENOUS VALVES IN VARICOSE VEINS

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INTRODUCTION

IN PATIENTS with varicose veins we are confronted by the phenomenon of a reversal of blood flow in the diseased vessels. This fact, though known to older surgeons, was first described in detail by Trendelenburg.[1] His name is given to the simple procedure which demonstrates the downward flow of blood in the abnormal saphenous vein under the influence of gravity. In some instances the test shows an additional abnormal reflux from the deep veins of the leg to the superficial saphenous system. It would seem that such an abnormal flow could hardly fail to have a deleterious effect on the nutrition of the extremity. We have never seen a case of varicose veins of the leg, with edema or ulceration, in which the Trendelenburg test failed to demonstrate downward reflux in the saphenous vein, with or without reflux from the deep veins.

The loss of this normal valve action, with a resulting abnormal blood flow, is characteristic of all high-grade varices. The downward flow of blood in the saphenous vein, or the outward reflux in the perforating veins, is caused by insufficiency of the valves which are normally present in these veins, intended in the former instance to direct the blood toward the femoral opening, and, in the latter, toward the deep veins (Fig. 1). As in the case of the aortic valve, two possibilities are present: (1) that this insufficiency results from primary disease of the valve cusp, as in rheumatic fever; or (2) that the insufficiency is relative, and is caused by a primary widening of the vessel, as in syphilitic aortitis. No conclusive data bearing on this problem are to be found in the literature. There is a paucity of direct, gross observations of the valves of varicose veins, and, as far as we have been able to discover, no histologic observations have been made.

In this paper are presented the results of microscopic examination of the valves in the upper end of the saphenous vein. The valves of 51 normal and 106 varicose saphenous veins were studied. All of the normal, and twenty-eight of the varicose, veins were obtained at autopsy. The remaining varicose veins were obtained at operation (high saphenous ligation) from individuals who were private patients of one of us (E. A. E.). Their ages varied from 21 to 72 years, and the known duration of the varices was from 2 to 40 years. In each patient incompetence of the valves had been demonstrated before operation.

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The removed portions of the saphenous veins were fixed in Zenker's solution or in formalin. Both longitudinal and cross sections were made of the valve cusp and the attached vein wall. A section of each was stained for elastic tissue by Verhoeff's method, and counterstained with van Gieson's connective tissue stain.* Mallory's phosphotungstic acid-hematoxylin stain was used additionally in some cases.

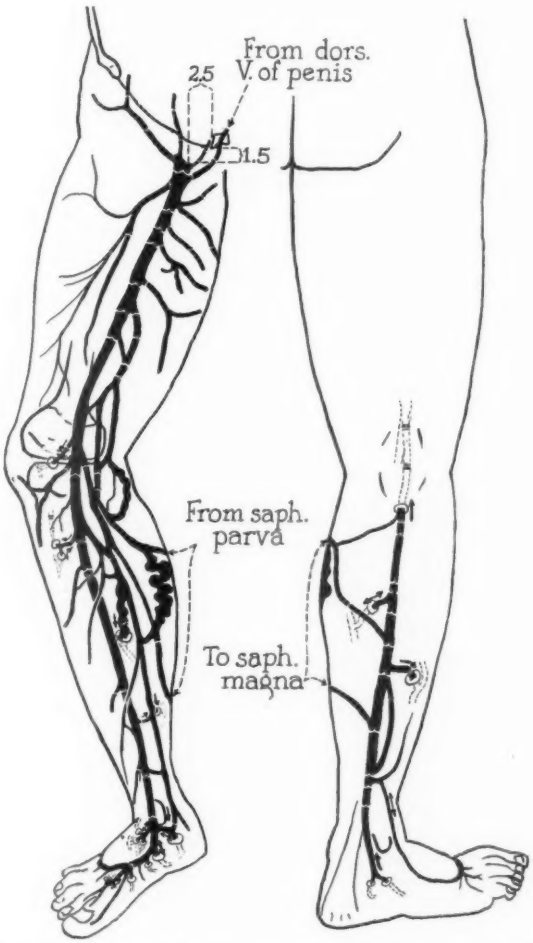


Fig. 1.—Dissection of the saphenous system. The veins are tributaries of the anteromedial (great) saphenous, and of the posterolateral (small) saphenous. The valves are indicated in white. The arrows indicate the direction of blood flow through the perforating veins. (From Surg. Gynec. and Obst. 59: 916, 1934.)

NORMAL ANATOMY

The following notes on the gross and microscopic anatomy of the saphenous valves are included to make the description of disease changes more understandable. They are not intended to cover the subject comprehensively.

*All of the photomicrographs shown in this paper were prepared from sections stained in this manner.

The entire saphenous system of veins is well supplied with valves (Figs. 1 and 2). Although they may be found at random, they are more likely to be located just below the entrance of tributaries. The mouth of each of these tributaries is likewise quite constantly supplied with a valve. These valves are set to direct the flow upward in the saphenous veins and tributaries. The veins that communicate (perforators) between the superficial and the deep veins are provided with valves directing the blood flow inward to the deep veins. This is true in the case of the thigh and the leg, but in the foot the perforators are likely to be without valves.

At a valve site, the cross section of the vein wall is elliptical in outline.[2] The cusps are attached to the wall parallel with the long axis of the ellipse (Fig. 17). To the outer side of each cusp lies the dilated space which is called the valve sinus. The segment of vein wall bounding the sinus is thinner than the rest of the vein. The attachment of the cusp to the vein wall lies close to that of its fellow in its proximal part, but diverges distally (Fig. 2). As in the case of the aortic valve, the region between the cusp attachments may be termed the commissure (Fig. 3). The vein wall is thickened at the commissure, forming a distinct projection into the lumen. This we propose to name the *commissural mound*. Each cusp is attached by its base to the inner edge of the mound. Moreover, the normal cusp projects directly across the vein lumen from one commissure to the other without any observable kink.

Fig. 2.—Model of a saphenous valve. The valve is bicuspid. Each cusp projects proximally.

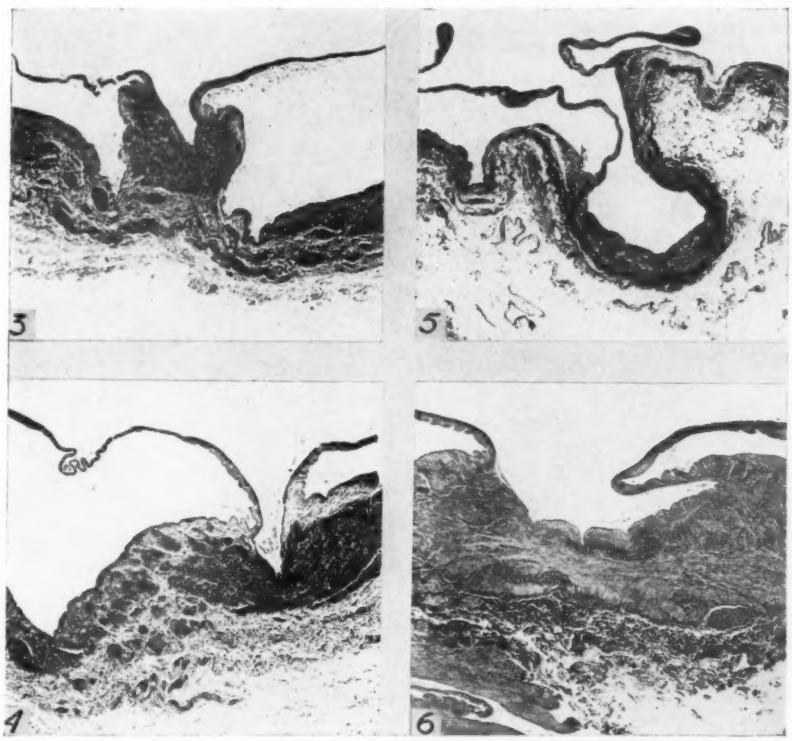
The cusp is composed of collagen, smooth muscle, and elastic tissue. The whole structure is clothed by endothelium, both on the sinus and the contact surface. The collagen is heavy at the base, thinning out toward the free edge of the cusp. The muscle is found in the basal quarter or third of the cusp, and is continuous with the longitudinal fibers of the subvalvular vein wall. The elastic tissue lies on the contact side of the cusp, forming a continuous membrane between the endothelium and the remainder of the cusp substance.[3] No elastic tissue is found on the

sinus surface. Moreover, the elastica of each cusp extends beneath the commissural endothelium to become continuous with that of its fellow.

THE VALVES OF VARICOSE VEINS

The type of lesion found in the valves of varicose veins depends on the etiology of the varices, as well as on complications occurring in the veins after the varicose process has been established. For this reason a brief clinical classification of the veins studied is in order. They may be divided into four groups, as follows:

Group 1 consists of varices of idiopathic origin, and forms the largest unit.



Figs. 3, 4, 5, and 6.—The primary dilatation changes in varicose veins. Transverse sections of saphenous veins at one commissure of each valve. ×20.

Fig. 3 is of a *normal vein.* Each cusp is attached to an inner corner of the wall thickening that we call the *commissural mound.* Beneath the endothelium of the mound there is a layer of elastica which is continuous with that of each cusp.

Figs. 4, 5, 6 show the primary commissural changes in the usual variety of varicosity. In Fig. 4, the mound has been effaced, and there is an evagination of the commissural wall. In Fig. 5, the commissural evagination has progressed to aneurysm formation. Fig. 6 shows a combination of evagination of the wall and widening of the commissure. The normal binding of the two halves of the vein is lost through rupture of the commissural elastica. The proximal part of the right cusp is bent toward its fellow. This deformity of the cusp is common when the commissure is widened.

Group 2 contains the postphlebitic varices, from patients in whom the antecedent phlebitis involved the deep veins of the thigh or leg, but had not progressed to the surface veins, or at least had not reached the upper part of the saphenous vein whose valves were examined.

Group 3 comprises a smaller number of postphlebitic varices from patients in whom the phlebitis had involved the upper saphenous vein, with or without a deep phlebitis.

Group 4 is made up of varices of either the first or second variety, from patients in whom a saphenous phlebitis had been superimposed after the frank development of the varicose state.

The lesions in the upper saphenous valves were found to be identical in Groups 1 and 2. Since these two groups include the majority of varicose veins, the changes to be described in them will later be referred to as the usual valve lesion.

In Group 3, consisting of the postphlebitic varices in which local saphenous phlebitis had occurred, a second type of valve damage was found. This lesion has already been reported in detail in a previous communication,[3] but will be referred to later in this paper.

In Group 4, the primary valve changes were obscured by the superimposed local phlebitis, and resembled those in Group 3, mentioned above.

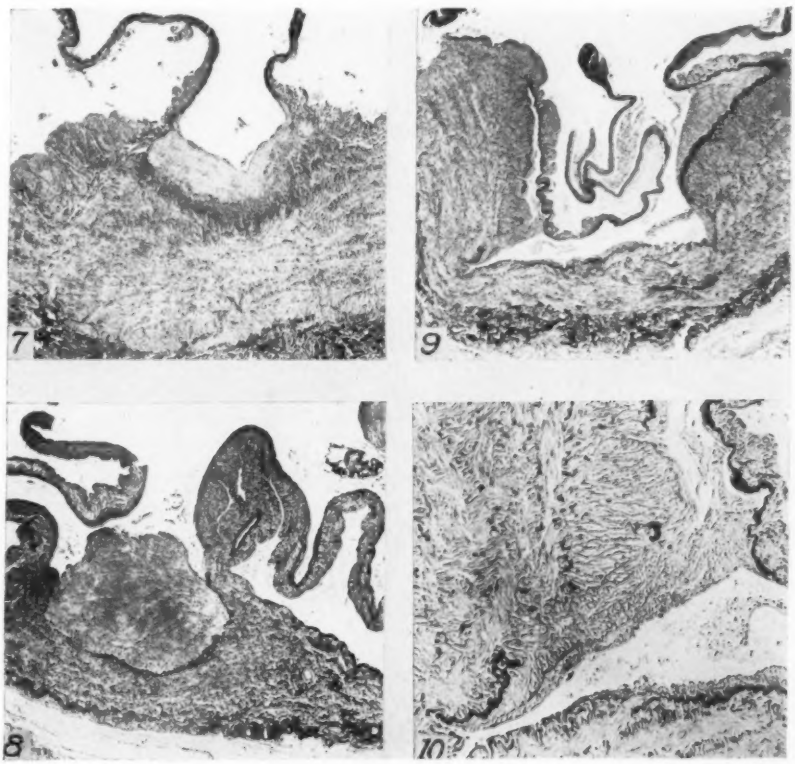
A. *The Valves in Idiopathic and Postphlebitic Varices Without Local Saphenous Phlebitis* (Groups 1 and 2).—The changes in the varicose saphenous vein can be divided into those in the vessel wall and those in the cusps proper. In every case studied there were changes in that portion of the wall which forms the commissure of the valve. The cusps, on the other hand, failed to reveal any constant lesions. The primary change in the commissure is dilatation of the wall; this is first seen as an evagination, which, in turn, is followed by widening, with a consequent separation of the cusp attachments (Figs. 4, 5, and 6). Secondary changes of a reparative nature are evident, but they are superimposed later in the process.

The process of evagination is seen in several stages, namely, effacement of the commissural mound, defect in the wall, and aneurysm formation. In the first stage of evagination, the heavy projection of tissue forming the mound thins out so that this part of the vein wall is no longer any heavier than that forming the sinus. The cusps now attach directly to the vein wall, rather than to a specialized portion of the wall, i.e., the mound. Since this constitutes the earliest stage of the disease, it is not frequently encountered. As a rule, the next stage, which consists of a defect in the wall, is commonly seen. The defect begins in the intima and extends well into the media (Fig. 4). It may be cleft-like, but since there is usually a concomitant widening of the commissure, the space between the cusp attachments becomes converted into a shallow recess. Occasionally, the accentuation of the defect produces an evagination of the entire wall to such an extent that it can truly be called an aneurysm (Fig. 5).

The widening of the commissure, with consequent separation of the cusps, nearly always accompanies the evagination (Fig. 6), and occurs

in a direction perpendicular to the force producing the commissural evagination. That the efficiency of the force of dilatation is not equal in the two diameters is obvious from the fact that one may see extreme aneurysm formation with only moderate widening of the commissure.

The separation of the cusps depends on the interruption of the normal binding power of the commissure. The tissues of this region ultimately become thinned out, and show actual breaks in continuity. This is best exemplified in the subendothelial elastica, the membrane connecting the elastic layer of one cusp to that of the other (Figs. 6, 7, 8, 9, and 10). In some sections the membrane is frayed out into fine bundles of elastic tissue, whereas in others there is fracture of the membrane, producing nu-



Figs. 7, 8, and 9.—The secondary, reparative, processes in varicose veins. Transverse sections of varicose saphenous veins, at one commissure of each valve. ×20. These are taken from patients who had the usual variety. In all, the sinuses are devoid of new tissue.

In Fig. 7, fibromuscular tissue has grown out of the wall to line the commissural evagination. The path of the tissue lies through the broken subendothelial commissural elastica.

Fig. 8 shows extreme overgrowth of a reactive tissue pad in the commissure. The unusual contour of the right cusp is caused by an artifact.

Fig. 9 shows evagination of the commissure, with extreme separation of the cusps. The reparative tissue binds the right cusp to the commissure. At the left, an adhesion connects the cusp and commissure. A new functional base is thus formed. The latter lies nearer to the other cusp than does the anatomic base.

Fig. 10 is a higher magnification of the adhesion between the left cusp and commissure of Fig. 9. ×87. The commissural elastica is fragmented, and through its fenestrations there is an outgrowth of the reparative tissue. This consists of smooth muscle and connective tissue.

merous fenestrations. This is apparently responsible for the characteristic changes in the sinus and cusp. Whereas the commissure is thinned and evaginated, the sinus, on the contrary, is thicker than normal and its width is greatly reduced. Furthermore, the cusp is now attached to the sinus segment of the wall, and since the width of the attachment of the cusp is diminished by the contracture of the sinus wall, the cusp becomes redundant (Fig. 17). It is likely that an added factor in the slackness is the loss of tone incident to the interruption of elastic and muscle tissue membranes. The redundancy allows a kinking of the cusp, and the lateral portions of this structure take on a characteristic change in shape. In the normal vein the cusp runs directly from its attachment at one commissure straight to the other commissure. In varicose vessels, however, the cusp does not extend in a straight line between its attachments, but is bent for a short distance toward the other cusp, then turns sharply as it continues in an irregular fashion toward its other attachment (Figs. 6, 9, and 17).

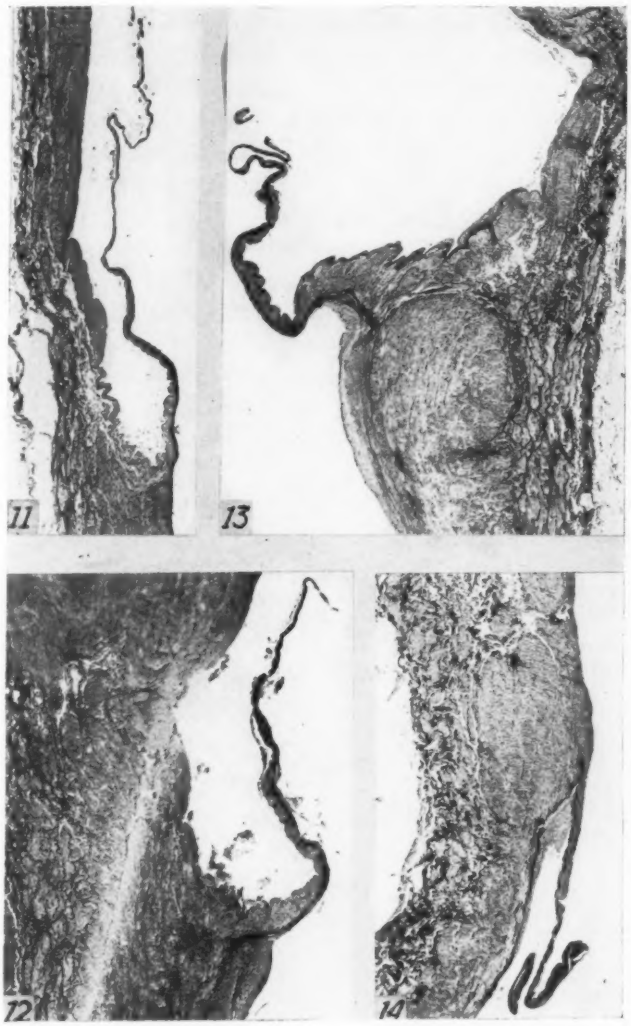
In the group of so-called normal veins there were occasional changes in the valve commissures differing only in degree from the ones seen in varicose veins. The most common changes were effacement of the commissural mound and, at times, minor degrees of evagination. In a few cases there was a slight degree of widening of the commissure, with a corresponding separation of the cusps.

The interruptions in continuity of the commissural tissue and, especially, the interruption of the subendothelial elastica seem to be a necessary antecedent to the development of the secondary or reparative processes. The reparative process is characterized by a growth of fibroblasts, an abundance of smooth muscle fibers, and a minimum of capillaries, through the fenestrations of the elastica upon the lumen surface of the now dilated and widened commissure (Figs. 9 and 10). As this tissue ages, the fibroblasts form heavy masses of collagen, and here and there fine shreds of new elastic tissue make their appearance. From its origin in the commissure the tissue may grow over the contact surface of each cusp, and may also grow downward in the subvalvular region of the wall (Figs. 12-14). This reparative tissue tends to compensate for the evagination of the commissure by filling in this part of the lumen.

Although the new tissue is frequently found in the evaginated commissure, it is not constantly present. When it is present, it varies from a thin layer beneath the endothelium (Fig. 7) to a heavy pad filling the evaginated commissure, and occasionally bulges into the lumen (Fig. 8). Moreover, the pad may vary in thickness in any one commissure, so that while it may project into the lumen at one point, it may be entirely lacking at another.

Adhesions of the contact surfaces of the cusps to the reactive tissue in the commissure ordinarily occur late in the disease. The adhesions may attach the cusp to the surface of the pad, or directly to the evagi-

nated venous wall (Fig. 9). In either case, the cusp is fixed in its characteristic bend toward its fellow, and a new functional base for each cusp is created. The pair now lie closer together than if they were to extend between the widely separated anatomic bases. The compensatory



Figs. 11, 12, 13, and 14.—The paucity of intrinsic cusp disease in the usual variety of varicosity. Longitudinal sections of saphenous valves. ×20.

Fig. 11 is from the same normal vein which was shown in transverse section in Fig. 3. The cusp is directed proximally. The sinus lies between it and the vein wall.

Figs. 12, 13, and 14 are from patients with varicose veins. The duration of the disease in these cases was 11, 30, and 40 years, respectively. In each case incompetence of the valves was demonstrated before operation. There is a uniform absence of profound, intrinsic, cusp disease. In each case, the reparative tissue has extended upon the contact surface of the basal part of the cusp. This is associated with a change in direction of the base of the cusp. In Figs. 12 and 13 there is a tendency toward a horizontal direction (perhaps due in part to the muscular hypertrophy of the venous wall). In Fig. 14, the entire cusp is completely reversed. The change in Fig. 14 is rare and is always associated with extreme commissural changes. The cusp of Fig. 12 is presented in transverse section in Fig. 7, and, likewise, that of Fig. 14 in Figs. 9 and 10.

mechanisms of padding of the commissure and advancement of the cusp attachments appear to be inadequate to overcome the effect of the evagination and widening, since we know that regurgitation takes place through these valves (Fig. 17).

While the reparative tissue may be of some theoretical advantage in overcoming the commissural changes, it may have a deleterious effect through its influence on the cusps. In some cases the reparative tissue extends on to the contact surface of the cusp. This produces a somewhat thicker and less pliable leaflet. Moreover, in certain instances the new tissue is associated with a change in the direction of the cusp. This can be seen in longitudinal sections. In the normal vein the cusp projects proximally from its base to its free margin. In the valves under consideration the basal part of the cusp may be bent so that it is directed horizontally (Figs. 11, 12, and 13). In rare instances an accentuation of the same change produces complete reversal of the direction of the cusps, so that they project distally from their attachment (Fig. 14). Even in such unusual cases the intrinsic structure of the cusp is essentially unaltered.

There is but one other change that we have encountered in the cusp. It consists of a rolling of the free margin similar to that seen in the aortic valve in syphilitic aortitis (Fig. 15).

Early in the disease the commissural wall external to the evagination may show thickening of its muscle. Later the entire commissure becomes thinned out.

B. *The Valves in Postphlebitic Varices with Antecedent Saphenous Phlebitis* (Group 3).—We have previously reported in detail on the fate of the valve in a segment of vein which is the seat of thrombophlebitis.[3] The changes all seriously damage the cusp. Thrombophlebitis of the saphenous vein affords an example of each of these lesions. When the thrombosis is complete, the cusps are disintegrated by the subsequent organization and recanalization. If the cusp happens to lie against the venous wall at the moment of thrombosis, it may simply be incorporated into the new, thick intima. In incomplete or parietal thrombosis, thickening, adhesions, or incorporation in the thickened wall will take place.

C. *The Valves of the Varicose Saphenous Vein after Superimposed Thrombophlebitis* (Group 4).—Thrombophlebitis may occur in a saphenous vein which is the seat of varicose changes of the spontaneous or usual postphlebitic variety.[4] When this occurs the nature of the original lesion is overshadowed by the same destruction or crippling of the cusps which is seen in any case of thrombophlebitis (Fig. 16).

DISCUSSION

Our studies indicate that the primary change in the usual type of saphenous vein varices is located in the vessel wall, and not in the valve

cusp. The characteristic regurgitation in varicose veins is a relative insufficiency, caused by lack of approximation of the valve cusps.

The opinion, based on clinical observations, that intrinsic damage to the cusp is not the cause of regurgitation in most cases of varicose veins has been expressed previously, especially by Bernsten[5] and Homans.[6] The latter author has seen the downward reflux in the saphenous vein disappear temporarily after simple bed rest, early in the course of the disease. We have had similar experiences with patients who showed incompetence of the valves of the saphenous vein and the perforators. After ligation of the saphenous vein in many such individuals, the veins narrow sufficiently so that the previously incompetent valves of the perforators become competent.

Elsewhere we have demonstrated how thrombophlebitis destroys or cripples venous valves which are caught in the thrombus.[3] We em-

Fig. 15.—Free edge of varicose saphenous valve cusp, showing bulbous thickening. Oblique section ×93. This is created by a rolling of the margin of the cusp. It is maintained in this position by fibrous tissue. This is the second cusp of the valve shown in Fig. 13.

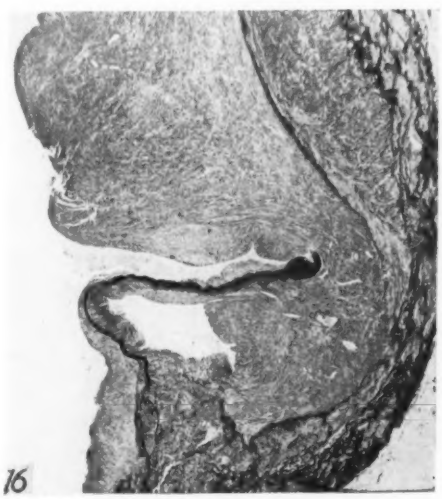


Fig. 16.—The valve of an ordinary, varicose saphenous vein which is the seat of mural thrombophlebitis. Longitudinal section, ×20. Much of the cusp is incorporated in the organized thrombus. This illustrates a lesion which damages the cusp proper.

phasized then that when varices develop after phlebitis the valves will often be so damaged *at the site of* the previous phlebitis. Usually, this means a loss of valves in the deep veins in the thigh or leg, as well as in the perforators. In the case of deep thrombophlebitis, however, involvement of the upper saphenous vein by the phlebitis proper is relatively uncommon. This vein is open, and acts as a collateral channel. Its dilatation produces a progressive, relative incompetence of the valves which is pathologically identical with the spontaneous variety. As indicated, if thrombophlebitis affects the saphenous vein there will be damage of the cusps through this local involvement.

Our observations cast some light on the nature of the pathogenesis of spontaneous varicosities: First, there is no evidence of *infection* or *inflammation* of the vein. Second, the veins show no signs of *antecedent thrombophlebitis*, except in the few cases of postphlebitic varices in which clinically recognized phlebitis had involved the upper saphenous vein. We found no thrombi in any of the other cases, which are classified in this paper as the spontaneous, and the usual postphlebitic, types. It may be asked if the tissue regarded as reparative in nature might represent organized thrombi. There are certain distinctions between the two types of tissue. An organized thrombus is located in the sinuses by choice; it is traversed by a rich network of blood vessels; phagocytic cells, laden with blood pigment, are present; and smooth muscle cells, if found within the mass, are minimal in number. The newly formed tissue in these specimens was located in the commissures only; it contained but few capillaries; no blood pigment was to be seen within its cells; and there was an abundance of smooth muscle tissue within it. Third, we found no evidence of a spontaneous degeneration of the valves. Such a process has been said to occur in adult life, and has been held responsible for the causation of varicose veins.[7] Fourth, we feel that the varicose change can be regarded as resulting from a disproportion between the venous pressure and the resisting force of the venous wall. We do not have at hand the facts necessary for a further discussion of the etiology. However, we may point out that once this disproportion exists, and dilatation begins, the latter follows in accordance with mechanical rules which are dictated by the anatomy of the vein. These rules determine the localization of the dilatation at the commissure, and, secondly, the tendency of the process to continue once it has begun.*

Reference should again be made to the elliptical shape of the vein at the valve site, and its compression here between the skin and underlying muscle and fascia. Dilatation in the shorter diameter of the cross

*We are indebted to Dr. Heinrich Peters, Professor of Fluid Mechanics at Massachusetts Institute of Technology, for stimulating and instructive consultation in this matter.

The relationship between the dilating and restraining forces can be expressed in the following formula:

$$\text{Stress (at any point of the vein wall)} = \frac{\text{Pressure (of the contained blood)} \times \text{Diameter}}{\text{Thickness (of the vein wall)}}$$

section is delayed and kept minimal by this compression, as well as by the buttressing of this segment by the line of the cusp attachment.

Dilatation in the longer diameter, that is, at each commissure, is counteracted externally only by the poor support of the subcutaneous fat. Moreover, the shape of the ellipse is a second factor tending to increase the dilatation at the commissure. The internal pressure of a liquid is applied equally to every point of the containing vessel, and is perpendicular to the tangent of the vessel wall. This results in a component of force which tends to separate the sinus and commissural segments of the vein. The stress is thus unequally distributed, and is maximal at the commissure. Under static conditions, every material has a definite elastic limit, beyond which plastic deformation, and, finally, rupture, take place. The commissural elastica is subjected to these changes and becomes evaginated. Each sinus segment of the wall, buttressed by its attached cusp, undergoes no stretching, but rather a contracture, and separates, as a distinct lamina, from its fellow sinus segment.

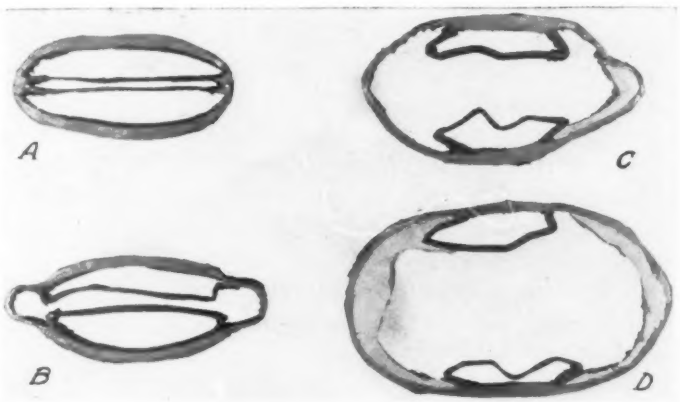


Fig. 17.—The progression of the varicose change; models of cross sections of the saphenous vein and valve. The valvular incompetence is caused by dilatation of these veins, rather than by intrinsic cusp disease.

In *A* the vein is normal. *B* shows the early change. The dilatation of the vein is localized at the commissure. In *C* and *D* the process has continued to a wide separation between the cusps.

In *C* one commissure contains reparative tissue. In *D* this material is present in each commissure, but it fails to correct the cusp separation effectively.

Once started, the dilatation in the commissural region tends to be irreversible, and is, indeed, progressive and accelerative. This is caused, first, by weakening of the wall through thinning and loss of continuity of its elastic membranes; and second, by progressive increase in the dilating force. This increase arises from the fact that the force directed laterally on a segment of a vessel is proportional to its long diameter. Since the evagination increases the diameter, the dilating force is likewise greater. A third factor in the progression of the disease is the slight, but early, regurgitation through the evagination. In this region there is a flow distally when the valve is closed, and a flow

proximally when the blood current is moving toward the heart before the valve has had time to open. This local flow sets up whorls in the blood. Obeying the recognized principles of mechanics, such whorls create vibrations in the venous wall. Vibration diminishes the elastic limit of any material, and the plastic state and rupture therefore occur earlier.

The reparative process may strengthen a thinned commissural wall, and at times fill an evagination and create new, functional, cusp bases. It has pathologic interest, but the clinical evidence indicates that it can never successfully approximate the separated cusps.

In view of the fact that some of the so-called normal veins contain valves showing changes similar to the early processes present in varicose veins, the following may be said: There are undoubtedly early pathologic changes in valves which differ only in degree from the well-established changes. These are merely insufficiently advanced to yield grossly evident varicosities.

SUMMARY AND CONCLUSIONS

The valves in the upper ends of varicose saphenous veins have been studied histologically. The valves of normal veins were also examined for comparison. This work was undertaken in an attempt to discover the pathologic changes that produce the valvular incompetence which characterizes varicose veins. The lesions vary in the different varieties of varicose veins. Most of the varices are either spontaneous in origin, or follow phlebitis of the deep veins. In these two groups of varices the valve cusps show no profound intrinsic lesions. The fundamental lesion is a dilatation of the commissural region, that is, the portion of the wall between the attachment of the valve cusps. This gives rise to an evagination of the wall and a separation of the cusps. Secondary changes of a reparative nature are seen. These consist of a growth of fibromuscular tissue upon the lumen surface of the dilated commissure.

The cusps show some extrinsic changes dependent on the primary wall lesion. These consist of: (1) relaxation of the cusp with redundancy and kinking, (2) occasionally, rolling of the free margin of the cusp, and, (3) in a few severe cases, a distal eversion of the cusp.

In a smaller number of varicose veins an antecedent, deep, thrombophlebitis had also attacked the portion of the saphenous vein which we examined. These cases are few in number; they illustrate destruction or crippling of the cusp by the local thrombophlebitis. The same destructive changes of the cusp are seen in thrombophlebitis complicating established saphenous varicosities.

In some so-called normal veins, early changes similar in nature to those present in varicose veins are seen.

We conclude that the regurgitation of blood in the upper saphenous vein, in the usual variety of varicosity, is secondary to a relative insufficiency of the valves dependent on the dilatation of the vein wall.

Moreover, our study indicates that the etiology of varicose veins is to be sought in the disproportion between the venous pressure and the resistance of the vein wall.

The usual type of varicosity is not caused by local infection or inflammation, thrombophlebitis, or spontaneous degeneration of valves.

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THE PATHOGENESIS OF BACTERIAL ENDOCARDITIS

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INTRODUCTION

INASMUCH as bacterial endocarditis is the cause of death in a large number of patients with heart disease, it challenges medical investigators to develop a method for its prevention and treatment. It is well, therefore, to pause occasionally and review the facts which have been established by clinical observation and experimental studies of this highly fatal disease. In this way it may be possible to acquire information which will be helpful both in prevention and treatment. I wish to review some of my own experiences with, and studies of, this disorder, and to summarize some of the facts concerning its pathogenesis.

ETIOLOGY OF BACTERIAL ENDOCARDITIS

It is now well recognized that infections of the heart valves may be caused by a wide variety of organisms; the commonest are streptococci, staphylococci, pneumococci, influenza bacilli, and gonococci. However, other organisms which are responsible occasionally include meningococci, *Neisseria pharyngis sicca, Bacillus "X," B. melitensis, B. coli,* and *B. suipestifer.*

For purposes of clinical description, bacterial endocarditis is generally classified as acute and subacute, or chronic, depending on its course. Although in most cases of subacute or chronic bacterial endocarditis the cause is a nonhemolytic streptococcus, or the *Streptococcus viridans,* there are other organisms which infect the valves and cause a relatively protracted disease. It is well, then, to classify each case both anatomically and etiologically, rather than by the clinical course.

CLINICAL FEATURES OF BACTERIAL ENDOCARDITIS

The clinical features of fully developed bacterial endocarditis are so well known that they require no discussion. The symptoms and signs of a chronic infection, the local signs of valvular heart disease, embolic phenomena, and bacteriemia usually suffice for the diagnosis. The cases in which the diagnosis is often difficult are: (1) those in which there is no bacteriemia; (2) those in which the disease is active, but in which no signs of valvular disease are present; and (3) those in which there is no bacteriemia or valvular disease. In a previous paper,[1] I discussed cases of bacterial endocarditis in which the disease was active without bacteriemia, and, at that time, I stressed the fact that about 20 to 25 per

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cent of all cases, as proved by post-mortem examination, belong in this group. In these, the diagnostic features of bacterial endocarditis, including valvular disease and embolic phenomena, were present. Clinically, it was possible to divide them into five groups: (1) patients with right-sided valvular disease, multiple pulmonary infarcts, and jaundice; (2) patients with renal insufficiency; (3) patients with heart failure; (4) patients with splenomegaly and anemia; and (5) patients with hemiplegia. In general, there was no essential difference in the clinical courses of the patients with bacteriemia and those without bacteriemia, with the exception of the fact that the latter were more likely to have renal insufficiency as an outstanding feature of their illness.

It scarcely seems necessary to say that bacterial endocarditis without bacteriemia must be distinguished from acute rheumatic endocarditis and from valvular disease with an associated infection elsewhere, without endocarditis or bacteriemia.

One of the characteristic features of acute rheumatic endocarditis is the absence of bacteriemia, although *Streptococcus viridans* bacteriemia has been observed during the course of acute rheumatic fever,[2] and the patients have no other signs of bacterial endocarditis and recover. Usually, these cases are assumed to be examples of acute rheumatic fever with transitory, intercurrent bacteriemia, for there are none of the other signs of bacterial endocarditis and the patients recover. It is not unlikely that some are actual examples of recovery from bacterial endocarditis, although at the present time there is no way of proving this contention.

As in the absence of bacteriemia, such features as the lack of progressive nephritis and of the signs of embolic phenomena, and the presence of pericarditis and cardiac arrhythmias, all point to rheumatic fever rather than endocarditis lenta. Usually the course of the disease settles the matter one way or another.

There is one other form of endocarditis which may be confused with both bacterial endocarditis without bacteriemia and rheumatic fever. This is the so-called indeterminate endocarditis, which was first described by Libman and Sacks.[3] Some of these cases are undoubtedly examples of acute lupus erythematosis disseminatus, with visceral manifestations. In these cases, the persistently negative blood cultures, the polyserositis, the progressive nephritis, the frequent absence of cardiac murmurs, and the characteristic skin eruption should enable one to distinguish the disease from either rheumatic fever or bacterial endocarditis.

Finally, bacterial endocarditis without bacteriemia must be distinguished from valvular disease associated with an infection elsewhere, without infective endocarditis. Such cases have been reported and discussed by Dr. George Herrmann,[4] who stresses both the importance of bacteriemia in the chain of evidence for the diagnosis of bacterial

endocarditis in such cases and the finding of evidence of infection in other areas in still others.

Usually the diagnosis is not difficult in these cases in which there is no bacteriemia if there are repeated emboli to various organs, splenomegaly, progressive nephritis, heart failure, or progressive anemia.

CASES OF BACTERIAL ENDOCARDITIS IN WHICH THERE ARE NO SIGNS OF VALVULAR DISEASE

Rarely one encounters cases of bacterial endocarditis in which there are no signs of valvular disease at any time during the course of the disease. In most cases, however, signs of valvular disease appear during the course of the disease if the patient survives six weeks or longer. The cases of bacterial endocarditis in which there is no bacteriemia are almost invariably instances of infection of previously normal heart valves, especially when the endocarditis is of the acute variety and the infection is of relatively short duration, so that the heart valves do not become insufficient through destruction. As a general rule, the endocarditis in these cases is only a part of a more widespread infection, with many metastases, or it occurs as a complication of some chronic disease, such as cirrhosis of the liver, ulcerating tumors of various organs, or leucemia.

Endocarditis may be suspected in the absence of signs of valvular heart disease if there is bacteriemia without an obvious focus of infection or emboli to various organs. If, during the course of the disease, a cardiac murmur appears, the diagnosis is more certain. I have seen several cases of bacterial endocarditis in which the vegetations were situated on the aortic valves below the line of closure and grew downward toward the mitral valve without ulceration. At necropsy, the vegetations were found to be located on previously normal valves, and there were no signs of destruction of the valves. Very often there were signs of infection for six or eight weeks, or longer. The infecting organism may be the gonococcus or pneumococcus.

CASES OF BACTERIAL ENDOCARDITIS IN WHICH THERE ARE NO CARDIAC MURMURS OR BACTERIEMIA

These cases are exceedingly rare, and the diagnosis is usually made by the pathologist. However, since they suggest certain points that are important in pathogenesis, they should be mentioned here. The cases that I have observed have been of a nature similar to those reported above, except for the fact that there is no bacteriemia. Of considerable significance are the cases in which there are an infective aortitis, with mycotic aneurysm formation (infective endaortitis), and no valvular murmurs until the aneurysm becomes large enough to cause deformity of the orifice of the aortic valve, when a murmur may appear. In such cases the blood cultures may be negative for several months.

Crane[5] has recently reported such a case, and Aschner[6] has recorded similar experiences with gonococcal infection.

THE PATHOGENESIS OF BACTERIAL ENDOCARDITIS

From the study of the pathogenesis of bacterial endocarditis in man and in experimental animals certain facts emerge. It now seems clear that such factors as (1) a previously damaged or injured heart valve, (2) the presence of platelet thrombi on the surface of the heart valves, (3) transient bacteriemia, and (4) the presence of antibodies which aid in sterilizing the blood and in the focalization of bacteria are all important in determining the development of bacterial endocarditis.

Bacterial endocarditis in man is most commonly encountered in those whose valves have been previously damaged as a result of an attack of rheumatic fever or of congenital heart disease. This seems to be true especially in the cases in which the disease is caused by the nonhemolytic streptococcus or other organisms of relatively low virulence. This is in striking contrast to the cases in which bacteria are implanted on normal valves, for in these the infection is likely to be caused by much more virulent organisms, and the disease process is usually much more acute.

In general, it can be said that bacterial endocarditis is rare when the preceding rheumatic infection has been only an attack of chorea, and it seems to be more frequent in patients who have chronic valvular heart disease and a normal rhythm. The persons who appear to be most vulnerable are those who are in good health, comparatively free of all symptoms suggesting heart failure, and who have not had repeated attacks of acute rheumatic fever. Patients with aortic regurgitation, alone or in combination with mitral valvular disease, seem to develop the disease more often than those with the characteristic signs of mitral stenosis. Indeed, the patients with mitral valvular disease who seem most likely to develop bacterial endocarditis are those with only a loud systolic mitral murmur. The disease is distinctly less frequent in patients with syphilitic aortic insufficiency than in patients with aortic valvular disease caused by rheumatic fever. However, within recent years more reports of bacterial endocarditis in patients with syphilitic aortitis and aortic insufficiency have been appearing. The subacute form of the disease is exceedingly uncommon in patients without previous cardiac murmurs and in persons with hypertensive heart disease. For some unknown reason, it is excessively rare in patients who have had attacks of heart failure or who have chronic auricular fibrillation. A single case has been recorded in which it followed a coronary artery occlusion which deformed the mitral valve by shortening the chordae tendineae.

The commonest congenital defects of the heart which predispose to infection are (1) congenitally bicuspid aortic valves and (2) patency of the ductus arteriosus, although the infection occurs in connection with

other defects, as well. Table I lists the various conditions of the valves with which bacterial endocarditis has been observed.

In a word, then, the patients with heart disease who are most likely to develop bacterial endocarditis are those with congenital heart disease or rheumatic valvular defects, who are in a good state of health and have a normal cardiac rhythm. Subacute bacterial endocarditis is not likely to develop in a person who has hypertension or a normal heart, or in anyone with established auricular fibrillation, or in a patient who has had an attack of congestive heart failure.

In addition to the valvular deformity itself, it is necessary to consider the various factors that predispose deformed valves to infection by bacteria. In other words, why do deformed valves make a favorable place for bacteria to focalize and survive? This matter has been studied and investigated by a number of persons, and in the main there are two views: first, that the heart valves are infected by bacterial emboli which focalize in the capillaries of the valves; and, second, that the organisms invade the valves from their surfaces.

TABLE I

CONDITIONS WITH WHICH BACTERIAL ENDOCARDITIS HAS BEEN OBSERVED IN MAN

1. Rheumatic Heart Disease, acute or chronic a. Aortic regurgitation b. Aortic regurgitation with mitral insufficiency c. Mitral stenosis d. Tricuspid insufficiency
2. Congenital Heart Disease a. Bicuspid aortic valve b. Patency of the ductus arteriosus c. Coaretation of aorta d. Subaortic stenosis e. Patency of the interventricular septum f. Pulmonary stenosis
3. Coronary Occlusion
4. Thrombotic Endocarditis (chronic disease)

The principal argument against the theory that the only mode of infection is embolic has been the failure to demonstrate blood vessels in the heart valves of all persons. Moreover, it can be demonstrated that bacterial infection of the heart valves is most often superficial, and that the bacteria occur at the periphery of the thrombi on the valves, and on valves without blood vessels. When very early bacterial lesions of the heart valves are studied, it is found that the microorganisms seem to invade the valves from the surface (Fig. 1). What is the mechanism by which bacteria gain a foothold on a deformed or injured valve? Certain evidence exists which suggests that, in many cases, at least, platelet thrombi on the surfaces of valves serve as a favorable environment for the localization of infection. Von Glahn and Pappenheimer[7] have expressed the opinion that most cases of subacute bacterial endocarditis result from an infection of rheumatic vegetations by micro-

organisms, and Grant, Wood, and Jones[8] have brought forth evidence of a most convincing nature that platelet thrombi are exceedingly common on damaged or injured valves and that these little platelet thrombi make peculiarly favorable areas for the localization of bacteria. In a study of nonbacterial thrombotic endocarditis, the same observers found that platelet thrombi occurred most often on valves which were thickened and deformed, and, furthermore, on the particular valves in which infective endocarditis is most likely to develop. In pursuing the question further, Grant and co-workers[8] found that platelet thrombi collected on the heart valves of animals following injury.

It occurred to me several years ago that, if platelet thrombi predispose to the development of bacterial endocarditis, we should be able to find bacterial endocarditis developing in cases in which nonbacterial thrombotic endocarditis frequently occurs. It is now known that nonbacterial thrombotic endocarditis occurs in a variety of conditions,[9] and I[1] have found that these thrombi may become infected and produce bacterial endocarditis. Table II summarizes the conditions in which I have observed noninfected and infected thrombotic endocarditis.

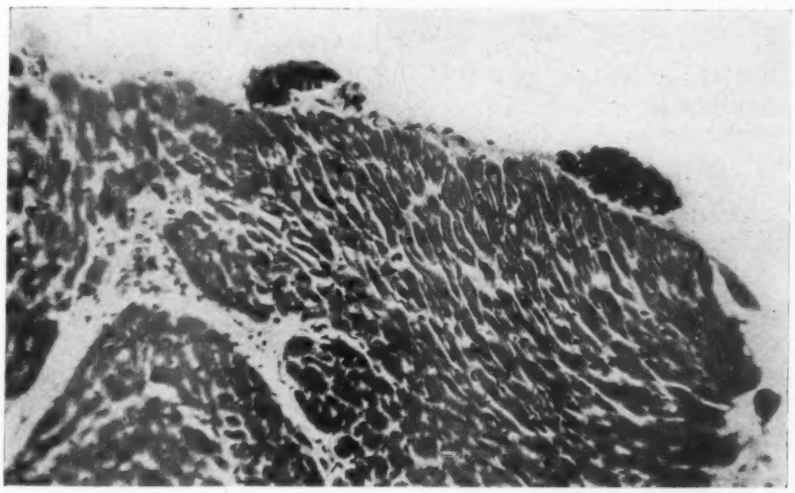

Fig. 1.—Section showing early vegetative endocarditis in a young patient with scarlet fever and hemolytic streptococcus bacteriemia.

It is well to recall that others have had this experience; Thayer[10] reported cases of bacterial endocarditis associated with chronic diseases which are not infrequently accompanied by nonbacterial endocarditis.

From numerous observations it seems plain that thrombotic and rheumatic endocarditis predispose to bacterial endocarditis because both afford a suitable area for bacteria to localize and gain a foothold, and, since such thrombi are relatively free of leucocytes, organisms focalizing here are able to survive. Inasmuch as we know, then, that bacterial endocarditis occurs very often in conditions which favor the develop-

TABLE II

NONINFECTED		NUMBER OF CASES	INFECTED		NUMBER OF CASES
Chronic heart disease		4	Chronic heart disease		2
Leucemia		2	Leucemia		2
Appendiceal abscess		1			
Pulmonary tuberculosis		3			
Cirrhosis of the liver		2	Cirrhosis of the liver		2
Cancer		4	Cancer		5
Penis	1		Cervix	1	
Uterus	1		Lung	2	
Stomach	2		Stomach	1	
			Kidney	1	
Cholangitis		1	Stone in common bile duct		1
Decubitus ulcers		2	Ulcerative colitis		1
Diabetes with tuberculosis		2			
Pneumonia		2			

ment of thrombi on the valve leaflets, it is not difficult to believe that these platelet thrombi are important in the pathogenesis of bacterial endocarditis.

Recent experimental studies by Friedman, Katz, Howell, Lindner, and Mendlowitz[11] have established the fact that streptococci grow freely in fibrin in vitro, and that the organisms are found in great numbers in the fibrinous thrombi on the heart valves. From the studies of Leary[12] and others, it would appear that the early vegetations occur on a bed of proliferating cells and soon become covered with fibrin and serve as a focus for bacteria.

BACTERIEMIA

Since bacterial endocarditis always follows a bacteremia, it is important to discover, if possible, the portal of entry and the conditions predisposing to the invasion of the blood. In many cases, it is impossible to find the portal of entry, and the endocarditis is well established before the patient comes under observation. Occasionally, the symptoms and signs of bacterial endocarditis first assert themselves following the extraction of teeth,[13, 14, 15, 16] tonsillectomy, respiratory infections, or infections with local areas of suppuration. Bacteriemia is known to be associated, at times, with all of these conditions. That nonhemolytic streptococci invade the blood in a variety of conditions has been amply demonstrated by Steiner,[16] Okell and Elliott,[17] Lichtman and Gross,[18] Epstein and Kugel,[19] Swift and Kinsella,[20] and others.

It is not surprising, then, that bacterial endocarditis may develop without a demonstrable preceding bacteriemia, for, by virtue of the fact that these organisms are normal inhabitants of the mouth and throat from a period shortly after birth until death, there are always opportunities for them to enter the blood stream in small numbers.

There are cases, however, in which the signs of bacterial endocarditis begin shortly after an infection that is often associated with bacteriemia, so that it is difficult to escape the conclusion that the

portal of entry was a recently recognized focus of infection. The following case is an example.

REPORT OF CASE

A 29-year-old married woman was well until two weeks preceding her admission to the hospital, when she developed endometritis following a self-induced abortion. This infection was treated by dilatation and curettage of the uterus, and she showed signs of progressive improvement for nine days. The day before admission to the hospital she began having a high fever and chilly sensations.

Examination showed that the patient was acutely ill, with a high fever, varying between 101° and 104° F., a pulse rate of 120 per minute, and a respiratory rate of 25 per minute. The heart was not enlarged, but there was a soft, blowing, systolic murmur along the left border of the sternum which increased in intensity as the pulmonic area was approached. The lungs were normal. The abdomen was moderately distended, and the liver and spleen were moderately enlarged.

Laboratory examination showed that the erythrocyte count was 3,600,000, the hemoglobin 58 per cent, and the leucocyte count 13,300. The blood culture on admission was negative.

Course of Illness.—During the three weeks that the patient was under observation, she had a high, irregular fever, frequent chills, marked prostration, and a progressive anemia. Her respiratory difficulty became more marked, and many fine râles appeared over the bases of the lungs. The liver became enlarged, and four days before death she became jaundiced, had repeated epistaxis, and showers of petechiae appeared over the chest and arms; the blood culture became positive for *Streptococcus viridans* the day before death.

Necropsy showed acute endocarditis of the tricuspid valve *(Streptococcus viridans);* multiple pulmonary infarcts; jaundice; chronic passive congestion of the liver; and multiple abscesses in the kidneys.

Comment.—This case illustrates several points. First of all, it is clear that the most likely portal of entry was the uterus; by the time she came to necropsy the local lesion in the pelvis had healed completely. Secondly, the clinical course illustrates the fact that endocarditis of the tricuspid valve may give very few localized physical signs, but is a source for multiple pulmonary emboli.

In any patient who is suspected of having bacterial endocarditis, it is well to inquire into the history for evidence of a preceding infection which might have been a portal of entry.

EXPERIMENTAL BACTERIAL ENDOCARDITIS

Bacterial endocarditis has been produced experimentally in dogs, horses, rabbits, and chickens, and the methods which are necessary to produce it successfully are of considerable interest in a consideration of the pathogenesis of bacterial endocarditis. For example, it has been ascertained that injury of the aortic valve alone, without injecting bacteria, may be followed by the development of bacterial endocarditis in a certain number of animals. Greater success is obtained by combining valve injury with the intravenous injection of live organisms, especially if the animal has been partially immunized, by means of vaccines, before the injection of bacteria. These observations suggest

that damage of the valve, bacteriemia, and the presence of immune bodies all play a part in the pathogenesis of the disease. In addition, it has been demonstrated by Grant, et al.,[8] that platelet thrombi form on the heart valves shortly after they are ruptured, and it is possible that such thrombi serve as a suitable medium for the localization of bacteria. In the cases in which bacterial endocarditis becomes superimposed on damaged valves, the situation is somewhat analogous to the conditions which favor the development of bacterial endocarditis in patients with previously damaged valves.

Bacterial endocarditis may also be produced experimentally without previous mechanical damage to the heart valves. This has been accomplished by repeated intravenous injections of bacteria. Wright[21] has been able to show that infection of the heart valves of rabbits is more likely to occur in animals that have been treated with vaccines, so that demonstrable antibodies are present in the circulating blood at the time of inoculation. These observations are in accord with those of Wadsworth,[22] who described bacterial endocarditis in horses which were being immunized against pneumococci. Of considerable significance was the fact that the valves became infected only after the antibody titer of the blood became high; there was no evidence that the infection took place early in the course of the injections. It was suggested by Wadsworth that the repeated injection of bacteria into the blood stream caused injury to the heart valves, so that they became more vulnerable to infection, especially when antibodies were present to aid in the clumping and localization of organisms. This equine endocarditis corresponds closely to the cases of endocarditis in man in which the lesions develop on previously normal heart valves, for most of the patients have had bacteriemia and have developed antibodies. It also resembles active bacterial endocarditis without bacteriemia, for Wadsworth was unable to grow organisms from the circulating blood of the horses, and there were very few organisms in the vegetations post mortem.

The recent observations of Friedman and his associates[11] suggested that infections of the heart valves begin in the fibrin thrombi that cover the proliferating cells of the damaged valve, and that the infection persists because the fibrin is a good culture medium and prevents the leucocytes from invading the vegetation.

In brief, it would appear that the production of bacterial endocarditis experimentally depended upon injury to the heart valves, bacteriemia, and immune bodies in the circulating blood. Similar conditions are also operative in man.

IMMUNOLOGIC REACTIONS IN BACTERIAL ENDOCARDITIS

It is now known that streptococci are killed in human blood by the action of the serum and the leucocytes, and, during the course of

both experimental endocarditis in animals and the disease in man, one can demonstrate antibodies in the circulating blood. This is true even when the bacteriemia is increasing. There seems to be no doubt that the bacteriemia in bacterial endocarditis is due to the fact that organisms are discharged from the vegetations faster than they can be removed from the circulating blood. There is no evidence that they multiply in the blood. That this is correct seems to be proved by the remarkable case, reported by Hamman and Reinhoff,[23] of subacute *Streptococcus viridans* septicemia in which a cure was effected by excising an arteriovenous aneurysm of the external iliac artery and vein. In this case, the removal of the focus (bacterial vegetations in the aneurysm) was followed within several hours by complete disappearance of the organisms from the blood and recovery. An appreciation of the fact that the body possesses an immune mechanism which is capable of clearing the blood of organisms serves to emphasize the utter futility of trying to treat this disease with vaccines, immune serum, or blood transfusions. There is nothing wrong with the immune mechanism insofar as the circulating antibodies are concerned, but the difficulty of destroying the organisms lies in the fact that they are capable of surviving in the vegetations. Their survival is made possible by the building up of a wall of fibrin in the vegetation that serves two purposes. It is a suitable medium for the growth of the organisms, and it prevents the invasion of leucocytes. Friedman and his associates[11] have shown quite clearly that the fate of the infected focus in the heart is determined by the balance between the amount of fibrin deposited and the granulation tissue ingrowth, for infected foci in areas other than the heart were sterilized by means of leucocytic invasion and walling off of the focus by granulation tissue. The possibilities, then, for sterilization of vegetations on the heart valves would appear to be as follows: (1) the actual destruction of vegetations by chemical agents, or (2) the prevention of deposits of fibrin. If this can be accomplished, there is no reason why the patient should not recover.

HEALING AND HEALED BACTERIAL ENDOCARDITIS

Under the classification of healing or healed bacterial endocarditis, Libman[24] described the bacteria-free stage of the disease. This term referred to patients who have gone through the bacterial stage and have lost the infection, but have sequelae, such as subacute and chronic glomerular nephritis, progressive anemia, embolism, and splenomegaly. In other words, they are patients who recover from the infection of the heart valves, but die as a result of the damage that has been inflicted during the active, infective stage of the disease. There are still other cases in which there is evidence at the postmortem examination of healed bacterial endocarditis without any of the above sequelae, and it has been suggested that these are cases of bacterial endocarditis in which recovery occurred.[24-26] How often

facterial endocarditis heals and is mistaken for chronic rheumatic valvular disease or acute rheumatic fever with intercurrent bacteriemia is a difficult matter to decide at present. That some patients recover from the disease there is no question; the only problem that arises at present is how often it happens, and how can one detect the mild cases in which spontaneous recovery is likely to occur.

COMMENT

From this discussion, it would seem justifiable to conclude that bacterial endocarditis in man, as well as in the experimental animal, results from damage to the heart valve, the presence of platelet and fibrin thrombi on the valve leaflets, a transient bacteriemia, and the presence of antibodies that favor the localization of bacteria. The treatment of bacterial endocarditis must have as its objective the destruction of the organisms in the vegetations, and it seems likely that this will ultimately be accomplished by means of chemotherapeutic agents.

SUMMARY

The various clinical aspects of bacterial endocarditis are reviewed, and the pathogenesis of the disease as it occurs in man and animals is summarized.

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Corrigendum

In the November, 1939, issue of the Journal, volume 18, page 603, the discussion by Dr. Taquini should have read as follows:

Dr. Taquini (closing).—We have not found any vascular constriction with plasma of blood taken from the vein of a normal kidney or from the general circulation, but with plasma taken directly from the ischemic kidneys of dogs we obtained a wonderful vasoconstricting action in every single case. I have all the results here and I shall read some of them. The figures represent the rate of perfusion in the Läwen-Trendelenburg preparation. The animal used in these experiments was the toad, *Bufo arenarum*, Hensel. In the first experiment, the number of drops per minute during perfusion with Ringer's solution was 60; with plasma from the renal vein of a normal kidney, 66; and with plasma from the totally ischemic kidney, 14. That means a diminution of about 65 per cent. In the second experiment, the number of drops with Ringer's solution was 71 per minute; with plasma from the renal vein of a normal kidney, 75; and with plasma from the totally ischemic kidney, 2, which is a diminution of about 95 per cent. In the third experiment, the number of drops with Ringer's solution was 56; with normal plasma, 63; and with plasma from the totally ischemic kidney, 7. All subsequent experiments gave similar results. In every case the vasoconstriction disappeared when Ringer's solution or normal plasma was perfused at the end of the experiment.

The fact that the plasma of venous blood taken from the ischemic kidney exerts a vasoconstrictor effect has been confirmed by direct perfusion of the legs of normal dogs. In agreement with these experiments, showing that there is a vasoconstrictor substance in the plasma of blood taken from the ischemic kidney, are those of Braun-Menéndez and Fasciolo. They found that the injection of 100 c.c. of blood from the normal kidney does not produce any change in the blood pressure of a normal dog, but there was a marked increase in the blood pressure following injection of the same amount of blood from the totally ischemic kidney.

Department of Clinical Reports

TRANSITIONS BETWEEN NORMAL INTRAVENTRICULAR CONDUCTION, BUNDLE BRANCH BLOCK, AND VENTRICULAR TACHYCARDIA

Report of a Case

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AMONG the gradually increasing number of cases of paroxysmal bundle branch block associated with heart disease that have been reported in the past few years, there have been numerous examples of abrupt changes between bundle branch block and normal intraventricular conduction. The following case is of unusual interest because of the electrocardiographic observations, which reveal the actual transitions between normal intraventricular conduction, bundle branch block, and ventricular tachycardia.

REPORT OF CASE

M. B. (Case 172064), a woman, 70 years of age, was admitted to the Rhode Island Hospital Feb. 21, 1935, and died the same day.

The patient was apparently well until three months prior to admission to the hospital, when she experienced a sudden attack of breathlessness while playing cards. She was treated by her private physician for cardiac decompensation, but, in spite of bed rest and increasing doses of digitalis, she became progressively more dyspneic and orthopneic and developed edema of the extremities. Two months before entry she developed a cough which was productive of rusty sputum, and complained of palpitation. During the next two months she became markedly edematous and developed oliguria. Because of the increasing severity of symptoms, she was finally brought into the hospital.

Physical examination on admission to the hospital revealed a very obese woman who was markedly cyanotic, had severe dyspnea and orthopnea, and was evidently acutely ill. The skin was cold and clammy. The veins of the neck were engorged. The lower two-thirds of both lungs posteriorly were dull to percussion, and over these areas, and also anteriorly over both lungs, there were medium and coarse moist râles. Bubbling tracheal râles were also present. The size of the heart could not be ascertained, and the heart sounds were obscured by the pulmonary sounds. The blood pressure was 80/60. The abdomen was protuberant, and there was shifting dullness in the flanks. A firm liver edge was palpable 5 cm. below the right costal margin in the midclavicular line. The spleen was not felt. The extremities were cold, and there was edema of the lower extremities from the knees down and over the sacrum. The temperature was 100.6° F., and the respiratory rate, 44 per minute. The pulse was rapid, irregular, and very feeble.

The patient failed to respond to therapeutic measures, became rapidly worse, and expired six hours after admission.

From the Heart Station of the Rhode Island Hospital (Director, Frank T. Fulton, M.D.), Providence, R. I.
Received for publication July 12, 1939.

Autopsy Report.—The heart weighed 630 grams. The tricuspid, pulmonic, mitral, and aortic valves measured 12.5 cm., 8.5 cm., 10 cm., and 7 cm., respectively, in circumference. Except for the mitral leaflets, which were the seat of minimal atheromatous thickenings, the valve cusps were thin, membranous, and translucent. The wall of the left ventricle measured 15 to 17 mm. in thickness, and that of the right ventricle, 3 mm. The cavities of both auricles and ventricles were of average size. The orifices of the coronary arteries were normal, their lumina were patent throughout, and the intima was smooth, gray, and glistening, except for a few 2 mm. areas of grayish-yellow thickening. In the interventricular septum, two-thirds of the distance from the ventricular base to the apex, there was an irregular, dark-red, soft area, 1.5 cm. in diameter, situated immediately adjacent to the cavity of the left ventricle, and extending 2 to 3 mm. into the papillary muscle at that point. Microscopically, in this area, the muscle fibers were undergoing necrosis, and showed uneven staining, a coarse granular cytoplasm, swelling of the nuclei with pyknosis and loss of many nuclei, and thinning of the fibers. The interstitial tissues between the muscle fibers were infiltrated by many erythrocytes, polymorphonuclear leucocytes, and a few lymphocytes and mononuclear cells. Scattered through the myocardium there were small areas of fibrosis, with vacuolization or loss of muscle fibers.

The rest of the examination revealed evidence of chronic passive congestion of the internal organs, with bilateral hydrothorax, partial atelectasis of both lungs, and multiple pulmonary and splenic infarcts.

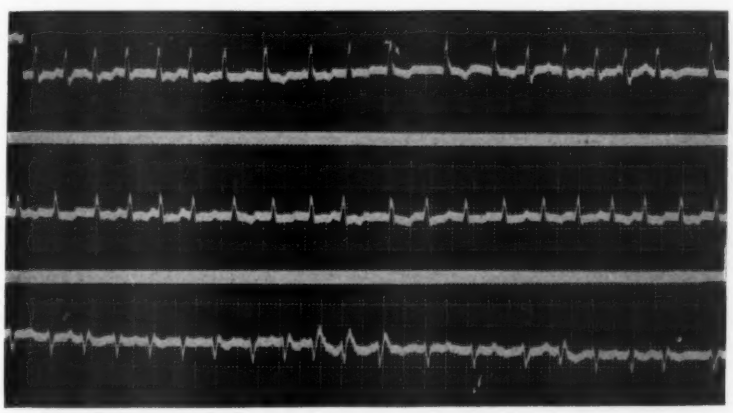

Fig. 1.—Electrocardiogram taken at 4:20 P.M. Auricular fibrillation, with ventricular rate of approximately 178 beats per minute.

CARDIAC MECHANISM

The original record (Fig. 1), taken at 4:20 P.M., shows auricular fibrillation with a ventricular rate of approximately 178 per minute, moderately low voltage of QRS, and left axis deviation. Near the end of Lead I, and in the middle of Lead III, there are several ventricular complexes with prolonged QRS intervals (0.12 to 0.14 sec.) and conspicuous slurring of the QRS deflections. The prominent S wave in Lead I indicates that these complexes represent transient right bundle branch block (Wilson).

Fig. 2 reveals a series of strips of Lead II in the order of their appearance, taken at intervals between 4:20 and 4:55 P.M. *B* shows the transi-

tion between bundle branch block and normal intraventricular conduction in the presence of auricular fibrillation. *C*, *D*, and *E* reveal pairs of ventricular extrasystoles, and, in *F*, the first short paroxysm of ventricular tachycardia, with a rate of 187 per minute, appears. The onset of the paroxysms in the presence of auricular fibrillation, the widened, aberrantly shaped ventricular complexes, the compensatory pauses fol-

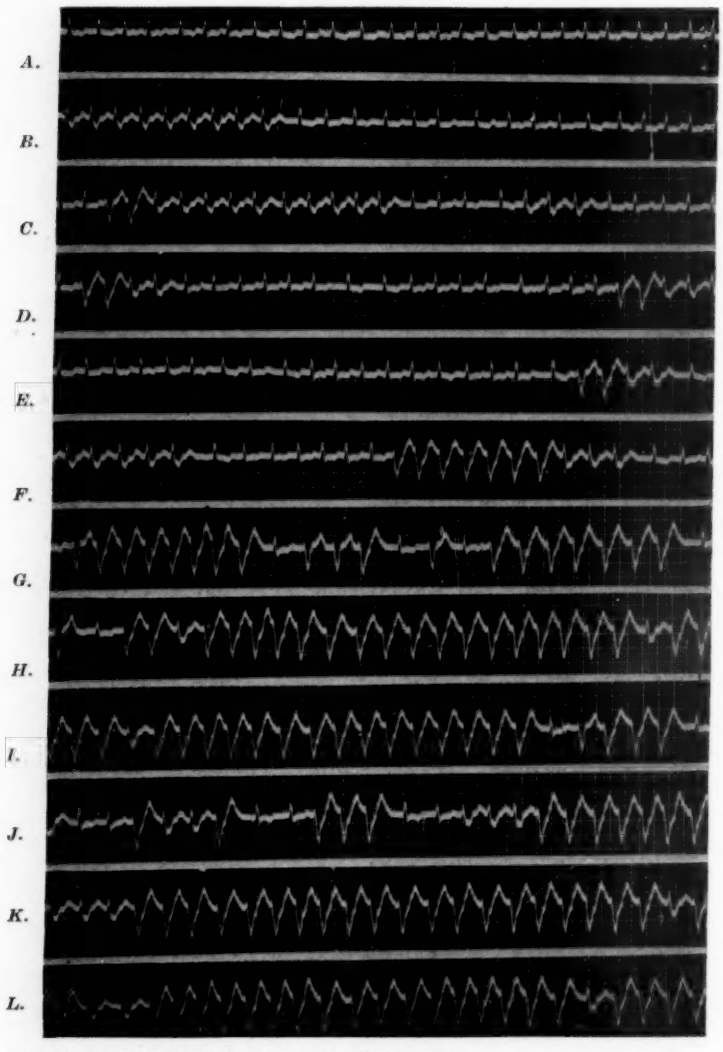

Fig. 2.—Tracings taken between 4:20 and 4:55 P.M.

A, Auricular fibrillation, with ventricular rate of 178 beats per minute.

B, Auricular fibrillation, with transition between bundle branch block and normal intraventricular conduction.

C, *D*, *E*, Transitions between bundle branch block, normal intraventricular conduction, and pairs of ventricular ectopic beats.

F, Appearance of paroxysm of ventricular tachycardia, with rate of 187 beats per minute.

G-L, Ventricular tachycardia alternating with ventricular ectopic beats, bundle branch block, and normal intraventricular conduction.

lowing many of the paroxysms, the variations in the ventricular rate, and the occurrence of ventricular ectopic beats similar in form to the complexes seen in the paroxysm are sufficient for a definite diagnosis of ventricular tachycardia. The paroxysms of tachycardia became progressively longer in successive tracings; they were interrupted occasionally by runs of complexes showing normal conduction and bundle branch block.

In Fig. 3 *A*, the three standard leads, taken at 5:25 P.M., reveal a slower ventricular rhythm, with a rate of approximately 143 per minute. In Fig. 3 *B*, Lead I, taken at 5:40 P.M., shows the bizarre, widened QRS complexes which frequently occur when the heart is dying. In Fig. 3 *C*, *D*, and *E*, Lead II, taken directly following the preceding (*B*), reveals a single-focus ectopic ventricular rhythm, with marked widening, slurring, and notching of the S wave, and progressively longer periods of cardiac standstill. The recording was continued for several minutes after the last tracing (*E*), but there was no further evidence of electrical activity.

DISCUSSION

It is difficult to evaluate the exact roles played by the various factors in producing the electrocardiographic changes in this case. Although there was an anatomic basis for the development of bundle branch block, in the form of a myocardial infarct involving the interventricular septum, the presence of normal intraventricular conduction at the time of the first electrocardiographic observation indicates that there was no permanent interference with the transmission of impulses in the conduction tissues. The various physiologic disturbances that have been postulated in an attempt to explain the mechanism of transient bundle branch block, such as anoxemia,[1, 2] vagal influence,[3, 4] myocardial fatigue,[5, 6] and disturbances in nutrition and impaired metabolism of the cardiac musculature associated with decompensation,[7, 8] were probably contributory, and the rapid ventricular rate which was associated with the auricular fibrillation was probably the precipitating factor in causing the defective bundle branch conduction.

Although much has been written on the subject of ventricular tachycardia, the mechanism involved in its production is not understood, and the problem regarding the site of origin of the arrhythmia still remains unsolved. Herrmann and Ashman[9] were the first to call attention to the theoretical possibility that ventricular tachycardia and fibrillation may occur in patients with transient bundle branch block. Their theory presupposes that these arrhythmias are the result of circus movement, initiated by depressed conduction as the impulse spreads through the interventricular wall to the ventricle whose bundle branch is blocked. Davis,[10] in his explanation of the mechanism of ventricular tachycardia, suggested that the arrhythmia was probably depend-

ent on some disturbance in the His-Tawara-Purkinje conduction system. This suggestion was based on the idea, elaborated by Davis and Sprague,[11] that the conduction system of the ventricle, because of its ability to conduct impulses rapidly to all portions of the ventricular musculature, created a state of refractoriness which tends to prevent an ectopic impulse in the ventricle from perpetuating itself through a process of re-excitation.

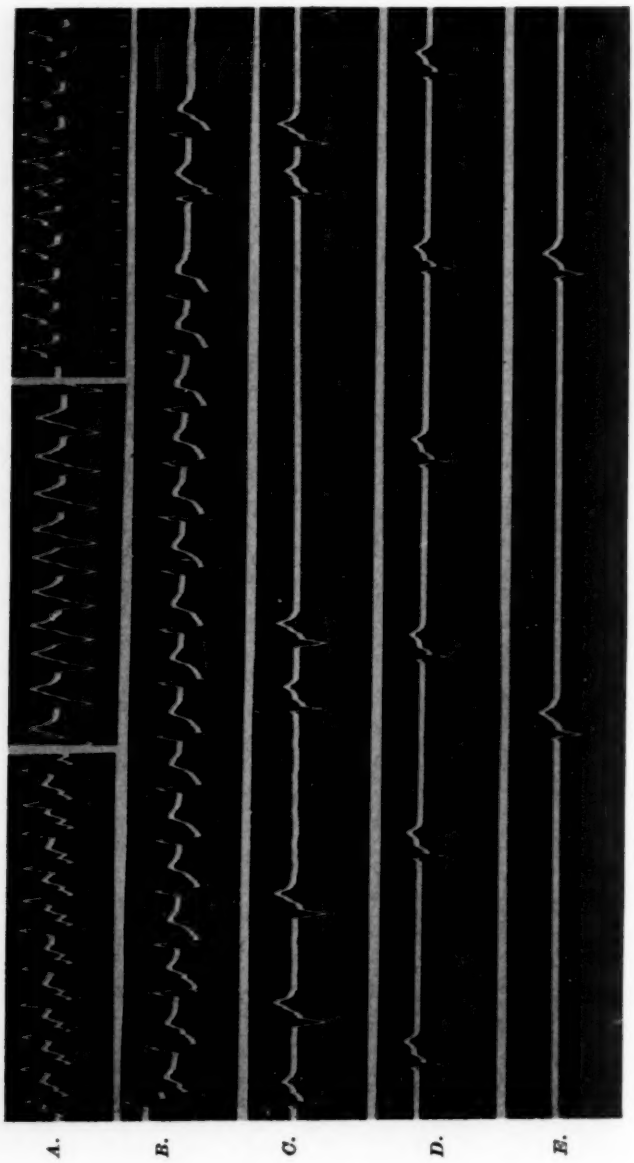

Fig. 3.—*A*, Three standard leads. Ventricular tachycardia, with a rate of 143 beats per minute. *B* (Lead I), Rate 91 per minute; same idioventricular pacemaker, with bizarre widening of the QRS complexes. *C*, *D*, *E* (Lead II), Progressively increasing periods of ventricular standstill, with final cessation of all electrical activity.

The present case lends further weight to the latter explanation of the mechanism of ventricular tachycardia. Of interest was the presence of at least two factors which depress conduction and are frequently associated with ventricular tachycardia, namely, excessive digitalization and disease of the bundle branches. The fact that digitalis produces block in the different portions of the conduction system has been adequately demonstrated, both experimentally[12] and clinically,[13] and Lundy and McLellan[14] have reported that excessive doses of digitalis were given in 36 per cent of the total of ninety-six accepted cases of ventricular tachycardia which had been reported up to 1934. The frequent association of ventricular tachycardia with septal infarction has suggested to some investigators[10, 15, 16] that damage to the conduction system, as well as irritability of the local area of infarction, is necessary for the production of this arrhythmia. Although the infarct of the septum did not at first interfere with the transmission of impulses, it is conceivable in our case that the rapidity of the heartbeat augmented the existent depression of the conduction tissues, so that conditions became suitable for the development of ventricular tachycardia.

Another unusual feature of this case was the mechanism of death. As pointed out by Grieco and Schwartz,[17] the belief that ventricular fibrillation is the terminal cardiac mechanism in all patients with ventricular tachycardia is based on very meager evidence. The sequence of ventricular tachycardia, ventricular fibrillation, and death has been reported but twice.[18, 19] In the case reported by Grieco and Schwartz,[17] bradycardia and ventricular standstill appeared as the terminal mechanism following ventricular tachycardia. They believe that ventricular tachycardia will terminate in ventricular standstill as frequently as in ventricular fibrillation. In our case, the tracings reveal gradual slowing of the ventricular rhythm, leading to progressively longer periods of ventricular standstill and, ultimately, to complete asystole.

SUMMARY

Electrocardiographic observations on a patient with myocardial infarction and severe cardiac decompensation revealed transitions between normal intraventricular conduction, bundle branch block, and ventricular tachycardia. The terminal cardiac mechanism was progressive slowing of the ventricular rate and ventricular standstill.

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Department of Reviews and Abstracts

Selected Abstracts

Rebensburg, H.: Animal Experiments on Lack of Oxygen and Asphyxia. II. Circulatory and Respiratory Changes in Asphyxia. Arch. f. Kreislaufforsch. 5: 123, 1939.

Asphyxia due to rebreathing without absorbing CO_2 produces no elevation of blood pressure in anesthetized dogs with their carotid sinus nerves and vagi cut, but only a drop; in addition, no pulse rate change occurs until terminal heart standstill. Respirations stop at about the same time as the heart. This is preceded by increased depth of breathing.

With these nerves intact, no changes occur until the CO_2 content exceeds 5 per cent and the O_2 falls below 12½ per cent in inspired air. After this point the blood pressure and pulse rate increase and reach their peak when CO_2 is 9.5 per cent and O_2 is 4.5 per cent. This indicates that the pressor and cardiac accelerator action of asphyxia operates on the chemo-receptors of the carotid sinuses and root of the aorta. Sectioning the vagi alone does not abolish the asphyxial blood pressure rise. When only a CO_2 increase is permitted and O_2 is kept at 20 per cent, neither the blood pressure rise nor the cardiac acceleration occurs.

KATZ.

Dietrich, S., and Dunker, E.: Observations of the Oscillations During the Heart Action. Arch. f. Kreislaufforsch. 5: 239, 1939.

A method of registering the oscillations of the heart occurring in an esophageal lead by means of four-stage radio amplification and condensor microphone is described (by W. Janovsky). By means of electrical filters these oscillations are separated into audible heart sounds and murmurs and into vibrations below the audible range. An attempt was made to correlate the latter with heart function. In the heart-lung preparation it was found that the magnitude and frequency of the subauditory oscillations increased when the magnitude of the left ventricular pressure development was increased. The velocity with which the systolic pressure is attained also has a similar effect. It is thus apparent that a damaged heart would have fewer and smaller oscillations.

KATZ.

Katz, L. N., and Steinitz, F. S.: Pulmonary Arterial Pressure in Experimental Renal Hypertension. Am. J. Physiol. 128: 433, 1940.

The pressure in the central pulmonary artery averages 28/11 and 28/9 mm. Hg, respectively, in normotensive and hypertensive trained unanesthetized dogs. The range of pressures in the former is $\frac{35 \text{ to } 25}{15 \text{ to } 7}$ mm. Hg and in the latter it is $\frac{37 \text{ to } 21}{18 \text{ to } 5}$ mm. Hg. A method is described for obtaining pulmonary pressures in trained unanesthetized dogs.

Systemic hypertension caused by renal ischemia does not alter the pulmonary pressure. This was demonstrated when readings were made both in anesthetized dogs with chest open and in trained unanesthetized dogs.

The humoral mediator appears to have a selective action on the systemic blood vessels and does not appear to act on the pulmonary vessels.

AUTHORS.

Wiggers, Carl J., and Wégria, René: Ventricular Fibrillation Due to Single, Localized Induction and Condenser Shocks Applied During the Vulnerable Phase of Ventricular Systole. Am. J. Physiol. **128:** 500, 1940.

Experimental evidence is reported which demonstrates that a brief induction or condenser shock applied to normal hearts of old or young dogs by stigmatic electrodes induces fibrillation only when the shocks fall during the vulnerable period of late systole. Since the effect is obtained by use of stigmatic electrodes, passage of the current through the whole or large parts of the myocardium is not necessary to initiate fibrillation.

Several implications are discussed: 1. Fibrillation following use of prolonged electrical currents, drugs, chemicals, and ischemia may likewise be induced by some effective stimulus—possibly a fortuitous one—falling during the vulnerable period. 2. One reason why an alternating current at critical voltages is more dangerous than the direct current seems to lie in the fact that effective variations of current strength obviously fall during the vulnerable phase in the former and only during closing and opening of the direct current. 3. The experimental results indicate that the effectiveness of currents or the variations of myocardial sensitivity to fibrillation cannot be tested experimentally by noting variations in the duration of current flow, a criterion frequently employed by previous investigators.

AUTHORS.

Hertzman, Alrick B., and Dillon, John B.: Selective Vascular Reaction Patterns in the Nasal Septum and Skin of the Extremities and Head. Am. J. Physiol. **127:** 671, 1939.

Evidence was presented that cutaneous vasoconstriction results from cold, painful stimuli, shock, fainting, mental effort and emotion, etc., while cutaneous vasodilatation results from local heat or from a rise in body temperature. Because of differences in the cutaneous blood supply and the varied reactions in the skin to changes in temperature and to drugs, it has been suggested that there may be a highly selective character of vascular activity or the existence of vasomotor patterns in the skin.

At a room temperature of 25° C., and after a rest period of twenty minutes, with the subject in the sitting position, the vascularity in the skin of the head, nasal septum, and extremities of healthy young males was observed by means of a photoelectric plethysmograph.

So-called spontaneous rhythmic waves in the plethysmograms were commonly seen. The majority of these waves seem to be due to vasomotor activity and possibly represent overshooting in vasomotor regulation, while some appear to be due to local activity of smooth muscle independent of the innervation.

Auditory and psychic stimuli, deep breaths, the cold pressor test, and breath-holding produced marked vasoconstrictor effects in the blood vessels of the skin of fingers, toes, and nasal septum, but the effects were variable in those of the ear and the head. The blood vessels of the skin of the ear were frequently constricted, but it was unusual to obtain a constrictor response in those of the forehead. The tendency of these latter vessels to dilate during vasoconstrictor reactions may be due to a rising blood pressure overcoming a weak constrictor effect or suggest a vasodilator reflex in this area.

These responses and the character, distribution, and timing of the spontaneous waves support the concept of vasomotor patterns in the circulation of the skin and nasal septum which are selective with respect to site, timing (whether the spontaneous waves were synchronous or not), and degree of vasoconstriction present.

ROTH.

v. Dungern, M.: Duration of Electrical Systole in Healthy School Children Before and After Exertion. Ztschr. f. Kreislaufforsch. **31**: 739, 1939.

Twenty-nine subjects were tested. Fridiricia formula Systole $= K \sqrt[3]{\text{cycle}}$ was used. K was found to be 8.15. After the exercise K decreased 3.8 per cent; that is, as the pulse speeded up, electrical systole shortened absolutely and relatively.

KATZ.

Sabathie, L. Gonzalez, and Fiorito, E. S.: Cardiovascular Tomography. Rev. argent. de cardiol. **6**: 209, 1939.

1. Left auricle and pulmonary veins.

The authors have analyzed the tomographies of normal subjects and of thirty-five patients with mitral disease (mitral stenosis, mitral stenosis with insufficiency, and mitral stenosis with aortic insufficiency). In normal cases the tomographies clearly show the right and left pulmonary veins which can both be followed through the projection of the cardiac shadow. In 70 per cent of the cases with mitral disease the right and left pulmonary veins are also well visualized, as well as the left auricle with both its borders, right and left. The left border is well identified because of the easy visualization of the left pulmonary veins. The trachea and its bifurcation are also made perfectly visible, this making the injection of lipiodol unnecessary for this purpose. In cases in which the right border of the heart shadow is formed by a very dilated left auricle, it is possible to identify through this shadow the right border of the right auricle.

The authors point out that apart from the valuable information obtained by this method in mitral disease, the identification of the pulmonary veins is of importance because: (1) it allows the recognition of their topography in vivo; (2) in doing so, difficulties and errors of interpretation in tomography of the lungs may be avoided; (3) by the identification of the left pulmonary veins the left border of the left auricle is easily recognized.

AUTHORS.

Mayerson, H. S., and Burch, G. E.: Relationships of Tissue (Subcutaneous and Intramuscular) and Venous Pressures to Syncope Induced in Man by Gravity. Am. J. Physiol. **128**: 258, 1940.

Venous (foot) and intramuscular (gastrocnemius) pressures in the resting, horizontal position are lower in individuals who develop postural syncope than in those who do not.

Tilting of individuals from the horizontal to the upright (75°) position is followed by immediate and simultaneous rises in venous, subcutaneous, and intramuscular pressures. Subjects who do not develop syncope show a secondary, usually more marked, increase in intramuscular pressure during the upright period, a change which is absent in those who show circulatory embarrassment.

Intramuscular pressure is affected by the tonus of the muscle fibers as well as the amount of intravascular and extravascular fluid present. When tonus is low, the value for intramuscular pressure tends to approach that of subcutaneous pressure.

Syncope does not occur in the upright position if any significant amount of tonus is evident. Likewise, increasing the tonus by muscular contraction eliminates all signs of syncope.

The development of syncope in the upright position is due primarily to a diminished venous return which leads secondarily to vasomotor failure.

AUTHORS.

Boisvert, Paul L.: The Streptococcal Antifibrinolysin Test in Clinical Use. J. Clin. Investigation **19**: 65, 1940.

The trends of repeated streptococcal antifibrinolysin tests in fifteen normal infants and children, six newborns, and 203 patients of the pediatric age group are reported.

The study suggests that, although a single test may be of no diagnostic value in the pediatric laboratory unless viewed in the light of the history and bacteriologic findings, the trend of several tests may be significant. The type of trend that was observed in the majority of patients with hemolytic streptococcal infections was found in no other type of disease.

AUTHOR.

Coelho, E., and De Oliveira, A.: Tachycardia and Paroxysmal Ventricular Fibrillation in Infarcts of the Myocardium. Cardiologia **3**: 169, 1939.

The authors report three cases of ventricular tachycardia and one case of ventricular fibrillation following cardiac infarction, the latter occurring in a patient 38 years old. The clinical symptoms in this case resembled a Stokes-Adams' attack. Several attacks occurred in this last patient, some being of the nature of ventricular tachycardia, until the patient finally developed a terminal ventricular fibrillation.

KATZ.

Ewert, B.: A Case of Partial Bundle Branch Block Which Appeared as an Arborization Block. Cardiologia **3**: 182, 1939.

A case is presented with acute normoblastosis and paroxysmal tachycardia, an arborization block which changed later to a bundle branch block (uncommon type). This fact is interpreted to indicate that the arborization contour was evidence of a partial bundle branch block.

KATZ.

Schocken, K.: The Validity of Einthoven's Triangle Rule. Cardiologia **3**: 197, 1939.

Synchronous points of three lead electrocardiograms in twenty patients were tested according to the Einthoven concept. Einthoven's triangle rule held approximately in 50 per cent and exactly in 20 per cent of these cases.

KATZ.

de Boer, S.: On the Nature of Fibrillation. Cardiologia **3**: 213, 1939.

Faradization of one auricular appendage caused auricular fibrillation. This was abolished by faradization or a single induction shock of the other appendage. This was done in ten cat hearts. The author believes this could occur only if a single circulating contraction were the mechanism responsible for the fibrillation.

KATZ.

Spühler, Otto: Recognition of S-A and Interauricular Block. Cardiologia 3: 244, 1939.

Fourteen cases of disturbances in intra-auricular conductivity seen in the course of a year are described. These included shortened P-R intervals, P wave abnormalities, resembling nodal rhythm. The absence of P waves as evidence of complete S-A block occurred rarely. Intermittent S-A block with Wenckebach periods preceding the dropped beat also were found. These occurred in coronary sclerosis, digitalis poisoning, and infectious processes. On the novel assumption that conduction from the sinus node to the ventricles is by a different path from that to the auricles, and that the path to the left auricle is different from that to the right, the author accounts for the prolongation and shortening of the P-R interval as well as for the notched and diphasic P waves.

KATZ.

Freundlich, J., and Lepeschkin, E.: Systemic Investigation of the Chest Leads in Normal Electrocardiogram. Cardiologia 3: 269, 1939.

Multiple precordial leads were analyzed in forty normal persons. Sixteen different positions on the anterior and posterior chest were used connected with the left leg. On the right anterior chest QRS is directed downward to become diphasic with first phase up over the apex. The T is inverted on the right side but becomes upright on passing to the left. In persons with a low diaphragm, QRS and T in the left fourth interspace is directed downward. These changes are correlated with the distribution of activity wave in the heart.

KATZ.

Groedel, Franz M., and Kisch, Bruno: Paroxysmal Ventricular Tachycardia With Morgagni-Adams-Stokes' Syndrome and Pre-Automatic Pause of the Sinus Node. Cardiologia 3: 301, 1939.

A case is reported in which short runs of ventricular tachycardia are interspersed among sinus beats during an attack. A "pre-automatic" pause occurs after the tachycardia before the sinus beats resume their control.

KATZ.

Herkel, W.: Observation of Aortic Isthmus Stenosis. Ztschr. f. Kreislaufforsch. 31: 729, 1939.

Three cases are described. In one there was a shift, with acceleration, from a sinus to an auricular rhythm. In the other two cases, a slowing of pulse wave velocity to the leg was noted.

KATZ.

Futcher, Palmer Howard: The Double Quotidian Temperature Curve of Gonococcal Endocarditis. A Diagnostic Aid. Am. J. M. Sc. 199: 23, 1940.

A study of the temperature charts of twenty-four patients suffering from gonococcal endocarditis showed that in eleven there was a striking double quotidian variation in fever lasting over a period of from five to twenty-two days.

AUTHOR.

Stewart, H. J., and Heuer, G. J.: Measurement of the Circulation in Chronic Constrictive Pericarditis Before and After Resection of the Pericardium. New York State J. Med. 39: 2183, 1939.

Twelve cases of chronic constrictive pericarditis were seen over a period of five years in New York Hospital. Ten of the twelve had resection of the peri-

cardium. The ten were observed before and after operation with reference to cardiac output by the acetylene method, vital capacity, electrocardiogram, arm-to-tongue circulation time (Decholin), venous pressure (direct method), roentgenogram of the heart at two meters, and infrared photographs of the peripheral veins. The results of these tests were all abnormal before operation and in every instance approached the normal levels following operation.

Operative technique is described. Three patients were cured, five cases improved by the operation. In one case it is too early to foretell results. One died nine months after operation.

McGovern.

Marcel, M. P.: Intermittent S-A Block in the Course of Acute Polyarticular Rheumatism. Cardiologia 3: 231, 1939.

Periodic changes in the P wave were observed in three acute attacks of rheumatic polyarthritis. This is attributed by the author to "partial and intermittent left-sided sino-auricular block."

Katz.

Struthers, R. R.: Rheumatic Heart Disease in Adolescence. Canad. M. A. J. 42: 128, 1940.

The author describes the clinical findings and course of thirty-five cases of rheumatic fever of the older school age group from 10 to 16 years. He emphasizes the importance of rheumatic fever and heart disease at this period of life.

McCulloch.

Klein, Reuben I., Levinson, Samuel A., and Rosenblum, Philip: Weltmann Reaction and Sedimentation Rate During Rheumatic Fever of Childhood. Am. J. Dis. Child. 59: 48, 1940.

The Weltmann reaction and the sedimentation rate were studied in 110 cases of rheumatic fever of childhood and in ten cases of subacute bacterial endocarditis. The rheumatic fever group was made up of twenty-six cases of chorea. thirty-two cases of acute rheumatic arthritis without carditis, thirty-nine of acute carditis, and thirteen of cardiac decompensation.

The sedimentation rate with chorea, although usually normal, may at times be increased. This increased rate may be related to a previous infection. The Weltmann reaction with chorea is almost always either normal or increased.

Acute rheumatic arthritis and carditis are characterized by a rapid sedimentation rate and a low coagulation band. The coagulation band returns to normal before the sedimentation rate.

In cases of cardiac decompensation the sedimentation rate tends to slow and the coagulation band tends to increase the values, depending on the severity of the decompensation in relation to the degree of infection.

The three pathologic stages of rheumatic fever, exudative, proliferative, and fibrotic, are reflected in the Weltmann reaction.

An increased sedimentation rate does not always mean that the rheumatic infection is still active. The patient may be convalescing, in a phase which is pathologically termed the proliferative stage, and still have a rapid sedimentation rate.

The Weltmann reaction is of value in the study of rheumatic fever, complementing the sedimentation rate; it may be of aid in the differentiation of subacute bacterial endocarditis from acute rheumatic carditis.

Authors.

Reichenfeld, L.: Miliary Tuberculosis and Tuberculosis of the Heart Muscle. Ztschr. f. Kreislaufforsch. **31**: 697, 1939.

An unusual case is reported of a long lasting miliary tuberculosis in a man 37 years of age who showed a Q_3 T_3 type of electrocardiogram. This was attributed during life to tuberculous involvement of the myocardium. This was confirmed at autopsy. A caseous infiltration as big as a bean was found in the right ventricle near the septum posteriorly, in addition to miliary lesions in the myocardium and pericardium.

KATZ.

Mulholland, S. W.: Hypertension's Challenge to Urology. J. Urology **42**: 957, 1939.

A frank discussion of the subject from the point of view of the urologist includes the work of Goldblatt, Page, Freeman, and others. Mulholland feels that hypertension is a symptom, the underlying causes of which are to be found, with few exceptions, in the kidney, and that the urologist should aid the clinician in relieving patients of their hypertension. Many cases are cited from his experience and from the literature where nephrectomy was performed because the hypertension was due to hydronephrosis or pyelonephrosis, and the patient was restored to health, the hypertension being completely relieved. He states that operative measures commonly undertaken today, such as sympathectomy, are not producing the long range results expected.

MCGOVERN.

Foucar, F. H.: Essential and Paroxysmal Hypertension, Contrasted by Case Reports. Am. J. Path. **15**: 741, 1939.

The case history and autopsy findings of a patient with essential hypertension are contrasted with the history and findings present in a patient with paroxysmal hypertension caused by a chromaffin cell tumor primary in the medullary portion of the adrenal. The differential clinical diagnosis is discussed.

NAIDE.

Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man. Bull. Johns Hopkins Hosp. **65**: 353, 1939.

On making a number of cross sections of the portions of the main renal arteries available for examination in a series of fifty cases of essential hypertension, arteriosclerotic plaques were found to project into the lumina of the arteries in forty-three cases (86 per cent). In most of the arteries the plaques were localized in segments of the vessels near the aorta; and they caused partial occlusion which varied from a moderate degree of constriction to marked stenosis of the vessels. In two cases, besides arteriosclerotic lesions, there were old thrombi which almost completely occluded the arteries.

The lumen of one or both of the main renal arteries was stenosed to a marked degree in twenty-seven cases (54 per cent). The difference between the inside and outside diameter of the narrow arteries in this group varied from four to six millimeters. In each of five of these cases both renal arteries were nearly occluded, and in eleven other cases one main renal artery was almost completely stenosed. The lumina of the very narrow arteries of these sixteen cases were reduced to small clefts each measuring 1.5 millimeters or less in width.

In a second group of sixteen cases (32 per cent) a moderate degree of stenosis of the lumen of one or of each main renal artery was found. The difference between the

inside and outside diameter of the moderately narrowed arteries varied from 3 to 3.5 millimeters.

In seven cases (14 per cent) the main renal arteries, so far as they could be examined, did not appear to be significantly narrowed. There was a difference between the inside and outside diameter of the arteries in this group which varied from 1 to 2.5 millimeters.

There was clinical and histologic evidence of vascular nephritis in twenty-eight of the cases (56 per cent). Little difference was found, however, in the incidence and degree of stenosis of the main renal arteries of the cases with and of those without nephritis.

In a group of cases in which there had been hypertension and renal insufficiency, and in which, therefore, the lesions of acute arteriolar necrosis might occur, it was found that the arteriolar lesions were present in 28 per cent of fourteen kidneys whose main renal arteries were very much narrowed (1.5 millimeters or less in width). On the contrary, acute arteriolar lesions were found in 87 per cent of thirty-nine kidneys whose main renal arteries were narrowed but measured more than 1.5 millimeters in least diameter. The higher incidence of arteriolar lesions in the latter group of kidneys suggests that the pathogenesis of the lesions may be similar in man and experimental animals.

In all of the cases of hypertension in this series the intrarenal arteries were the site of arteriosclerotic changes; and arteriosclerotic plaques were found to cause a marked degree of stenosis of the lumen of one or both of the main renal arteries in over half of the cases. It seems not unlikely that these arterial lesions may have caused sufficient partial occlusion of the renal arteries and their branches to induce chronic hypertension by the mechanism which Goldblatt and others have shown to be effective in experimental animals.

A degree of arteriosclerosis and stenosis of main renal arteries comparable to that seen in some of the cases of hypertension was found in five of the control cases (10 per cent). In each of these control cases the state of either the myocardium, kidneys, or renal arteries themselves was such as to appear to offer a reasonable explanation for the absence of hypertension.

AUTHOR.

Eden, Kenneth C.: The Vascular Complications of Cervical Ribs and First Thoracic Rib Abnormalities. Brit. J. Surg. 27: 111, 1939.

Three cases of dilatation and thrombosis of the subclavian artery as a result of cervical and first thoracic rib abnormalities are reported.

Evidence brought forward supports the hypothesis that the vascular disease of the arm in these cases is due to damage to the wall of the subclavian artery by intermittent compression between the clavicle and cervical rib or first thoracic rib. As a result, dilatation of the artery commonly occurs, with dense fibrosis around it and thrombosis. With continued trauma blood-clot is thrown off in the form of emboli, which lodge in the vessels of the hand and arm, giving rise to progressive thrombosis and symptoms of vascular disease.

The literature on the vascular complications of cervical ribs is reviewed. There are fewer instances of vascular complications than of nerve complications. In the case with a vascular complication the simplest procedure is removal of the cervical rib. Division of the scalenus anterior muscle alone is insufficient to prevent further trauma. Enough of the abnormal rib must be removed to allow the subclavian artery to pass freely beneath the clavicle without compression.

NAIDE.

deTakats, G., Beck, W. C., and Roth, E. A.: The Neurocirculatory Clinic. A Summary of Its Activities. I. Peripheral Vascular Disease. Ann. Int. Med. **13**: 957, 1939.

This is a review of the activities of the Neurocirculatory Clinic of Dr. deTakats during 1936 and 1937. The following vascular diseases were seen; fifty-four patients with Buerger's disease, 132 with obliterating arteriosclerosis, thirty-six with diabetic arteriosclerosis, and twenty-six with Raynaud's disease. These are further subdivided according to the stage of the disease in which the patient is first seen and treated. The rest of the paper is a reiteration of the conventional treatment of vascular disease and is similar to the review by Scupham, deTakats, and others appearing in the *Archives of Internal Medicine* in September, 1939.

McGovern.

Gitlow, S., and Goldmark, Carl: Generalized Capillary and Arteriolar Thromboses. Report of Two Cases With Discussion of the Literature. Ann. Int. Med. **13**: 1046, 1939.

Two cases presenting different clinical pictures but the same pathologic lesions in the small arterioles and capillaries in various organs throughout the body are described.

Case I: An 18-year-old girl showed evidence of severe anemia, purpura, icterus, and nephritis. Various diagnoses were made ante mortem, none of which was correct. The pathologic picture is one of extensive thrombosis in the smaller arterioles and capillaries.

Case II: A 27-year-old woman was diagnosed clinically as Lupus erythematosus with an accompanying cardiac lesion of the Libman-Sachs type. This diagnosis was confirmed at necropsy.

Microphotographs showed the pathologic lesions to be identical in these two cases. The review of the literature is well done and together with the authors' experience suggests that periarteritis nodosa may be related to, or a variant of, this condition of thrombosis of the capillaries and arterioles.

McGovern.

Applebaum, E., and Kalstein, M.: Periarteritis Nodosa; Report of Three Cases Diagnosed Clinically and Confirmed by Necropsy in Two Instances and Biopsy of the Third Case. New York State J. Med. **39**: 2553, 1939.

Three cases of periarteritis nodosa diagnosed ante mortem are presented, two of which were confirmed by post mortem examination and one by biopsy. Neither the case histories nor the autopsy reports are so complete as one would desire in this rare and difficultly diagnosed disease.

It is interesting that two papers on this subject appear this month in different periodicals, and in each a plea for early or at least ante-mortem diagnosis is made.

McGovern.

Ochsner, Alton, and DeBakey, Michael: Thrombophlebitis: The Role of Vasospasm in the Production of the Clinical Manifestations. J. A. M. A. **114**: 117, 1940.

The concept that mechanical blockage of the venous and lymphatic systems is of primary significance in the production of the clinical manifestations in thrombophlebitis is inadequate.

Based on recent clinical and experimental investigations, we believe that many of the symptoms and signs are due to vasospasm of the arterial and venous

systems and that the vasoconstricting impulses originate in the thrombophlebitic segment.

As the result of vasospasm there result increased filtration pressure, relative anoxia of the capillary endothelium, and diminution in the flow of lymph, all of which increase the amount of perivascular fluid.

By interrupting the vasoconstrictor impulses with procaine hydrochloride infiltration of the sympathetic ganglions, there is produced a re-establishment of the normal exchange of intravascular and perivascular fluids.

Fifteen patients with seventeen thrombophlebitic processes have been treated by procaine block of the sympathetics. These cases are characterized by the prompt and permanent relief of all clinical manifestations in contrast with the usual case of phlegmasia alba dolens, in which there is pyrexia for from four to six weeks and the likelihood of persistent undesirable sequelae such as edema, varicosities, and ulceration.

There was prompt and permanent relief of pain in all instances.

In half the cases the temperature returned to normal within forty-eight hours and in the other half within one week.

In more than half the cases the edema completely subsided in eight days and in the remaining ones within twelve days.

Sixty per cent of the patients were discharged from the hospital as cured within eight days after the institution of therapy.

AUTHORS.

Nelson, Marius, Herrington, L. P., and Winslow, C. E. A.: The Effect of Posture Upon Peripheral Circulation. Am. J. Physiol. 127: 573, 1939.

By means of partitional calorimetry and the use of the tilting table, the effect of passive postural changes upon the peripheral circulation of several normal individuals was observed.

Rectal temperature, skin temperature, O_2 consumption, loss of weight by evaporation, pulse rate and blood pressure were measured in a constant temperature room at two levels, 30° and 35.6° C. Passive change of body posture on a tilting table from the horizontal to a feet-down position (45° from horizontal) produced peripheral vasoconstriction, as indicated by a decrease in the temperature of the skin, over the main body surface in subjects not adapted to warm environment. The skin temperature of the toes changed in a direction opposite to that of the body, involving possibly a protective mechanism against local chilling. However, at a high tilting angle (70°) at which collapse was usual, both fingers and toes decreased in temperature with the general skin surface.

STEELE.

Schirrmeister, S.: Simultaneous Electrocardiographic and Histological Observations of the Heart in Low Pressure Chambers. Arch. f. Kreislaufforsch. 5: 264, 1939.

Guinea pigs were slowly exposed to low pressures equivalent to an altitude of 7,500 to 8,000 meters. In 100 hours the majority died. At autopsy numerous disseminated focal necroses were seen especially in the left ventricle.

In acute experiments with low pressures an acute coronary insufficiency causes similar necroses in the inner wall and apex of the left ventricle in both the rabbit and the guinea pig. The latter are more resistant to low pressures. These anatomical changes can be predicted from the characteristic electrocardiographic changes consisting of S-T depression and inversion of T in Leads I and II. The appearance of these electrocardiographic changes is not necessarily a sign of impending death.

The occurrence of these lesions in the left ventricle is attributed to the fact that the systemic blood pressure and heart rate are augmented by moderate lowering of the atmospheric pressure.

KATZ.

Evans, William, and Loughan, Owen: The Drug Treatment of Hyperpiesia. Brit. Heart J. 1: 199, 1939.

The effects of thirty-three clinical preparations were observed on the blood pressure and associated symptoms of seventy patients with uncomplicated hyperpiesia, thirteen of whom were males and fifty-seven females. This series included patients whose systolic blood pressure was more than 160 mm. of mercury and the diastolic pressure more than 100 mm. of mercury. No patient with nephritis was included in the group.

The clinical preparations which were used were: sodium nitrite, glyceryl trinitrate, erythrol tetranitrate, mannitol hexanitrate, bismuth subnitrate, potassium iodide, iodine, potassium bromide, sodium luminal, chloral hydrate, papaverine sulfate, euphyllin, diuretin, theominal, doryl, pacyl, hypotan, calcium chloride, atropine, potassium thiocyanate, benzyl benzoate, guipsine, detenxyl, phyllosan, citrin, yohimbine hydrochloride, padutin, vagotonine, angioxyl, bioglan H. anabolin, perandren, and oestrone. Each preparation was prescribed in optimum doses for a test period of two weeks and in a certain number of patients for a second longer period. Previous to, and at the end of, each period the blood pressure under standard conditions and changes in symptoms was observed. At irregular intervals, control test periods were instituted during which only an inert placebo mixture was given.

None of the thirty-three preparations was found to produce hypotensive effects any greater than those of an inert placebo preparation in patients with hyperpiesia. Symptomatic improvement greater than that shown during the use of a placebo preparation was found only following the use of six of the drugs, namely: bismuth subnitrate, iodine and iodide, bromide, sodium luminal, theominal and potassium thiocyanate. The sedative drugs seem to have value in temporarily relieving nervous symptoms when these are prominent.

A comparison of changes in the blood pressure and symptoms in response to the drugs failed to show any relation between symptoms and change in level of blood pressure. During sixty-four test periods when the blood pressure was increased more than 25 mm. of mercury, the symptoms were improved in 36 per cent of the patients, unchanged in 38 per cent and worse in 26 per cent. During ninety test periods when the blood pressure decreased more than 25 mm. of mercury, the symptoms were improved in 34 per cent of the patients, unchanged in 46 per cent and worse in 20 per cent. A clearer insight into the origin of hypertension must, apparently, precede its successful treatment with drugs.

ROTH.

Book Reviews

LE DÉBIT CARDIAQUE; ÉTUDES EXPÉRIMENTALES ET CLINIQUE: By Jean Lequime, Agrégé de l'Enseignement supérieur, Assistant à l'Université de Bruxelles. Paris, 1940, 210 pages, Masson et Cie.

Although perhaps it should be expected from the usual fate of prophets, the physiologic school of clinical medicine founded by Claude Bernard has had a smaller following in France than in most other countries. The reviewer is glad to see a representative of this school writing in French, even though the work was done, not in Paris, but in Brussels.

The book is excellent; it covers a large experience in estimating the cardiac output of patients by Grollman's acetylene method, somewhat modified in certain instances. Some of the conclusions are supported by animal experiments in which cardiac output was estimated by the Fick method. The literature is carefully reviewed. The clinical aspect of the cases is presented very fully.

The author's chief interest is in the effect on the cardiac output of modifications of the basal metabolic rate, diuresis, hypertension, and congestive heart failure. It is a pleasure to note that in most respects the results are similar to those reported by American authors. Only a few years ago this field was in confusion, but now, as a result of constant effort to improve technique, workers throughout the world are obtaining comparable results.

Lequime finds that the cardiac output in thyroid disease varies in the same direction as the metabolic rate, and that its deviation from the normal is proportionately greater. Iodine and thyroidectomy cause a return to, or toward, normal. After drinking large amounts of water the cardiac output increases more than after drinking similar amounts of saline solution. In hypertension the cardiac output is normal. In congestive failure the output is invariably reduced, and returns toward normal as the condition improves. Thus the author supports what might be called the classic view, in contrast to the position taken in this country by Harrison, i.e., that there is no invariable relation between cardiac output and congestive failure.

ISAAC STARR.

CARDÍOLOGIA: By Dr. Jorge Meneses Hoyos, Professor de Clinica de Enfermedades del Corazón, del Riñón, y de la Sangre en la Escuela Médico-Militar, etc., Mexico, D. F. Editorial Cultura, Mexico, 1939, 277 pages, 45 illustrations.

This book, apparently written for undergraduate students, describes briefly the principal diseases of the heart and blood vessels. More than a third of the volume is devoted to the anatomy and physiology of the heart and the technique of examination. Too much of the text consists of verbatim quotations from well-known textbooks. The illustrations are few, and not always clear. The phonocardiograms are unsatisfactory technically, and there are no mechanical tracings.

The review of the literature does not take into sufficient account many important European contributions, e.g., in the description of tricuspid stenosis.

The author's record of the normal Lead IV was evidently made with the old technique, whereas in the text only the new Lead IV F is described.

The author believes that "average pressure," as recorded by the method of Vaquez and Gley, has real clinical value; this assumption might be questioned.

The chapter on valvular defects is very short. The author maintains that the "double souffle" of Duroziez and the "Doppelton" of Traube are identical, but, in reality, they are quite different.

The description of aneurysms of the aorta occupies less than two pages, which is hardly adequate.

Angina pectoris and coronary occlusion are not considered together, and neither are arterial hypertension and hypertensive heart disease, which certainly does not facilitate differential diagnosis of the former or clinical study of the latter.

Obvious errors, such as "Gallop rhythm is easier to detect by palpation than by percussion" (page 39), should be corrected.

ALDO LUISADA.

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